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# **ASPECTS ON INTERVENTIONS IN COMPLICATED GALLSTONE DISEASE**

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Institutet**

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Front cover: **Frederici Ruyschii**, 1691. Observationum anatomico-chirurgicarum centuria.  
Original illustration of the gallbladder: A. vesica fellea humana. B. cellulæ in superficie interna. C. calculosa crusta.

Back cover: **William White**, 1777. An Essay on the diseases of the bile, more particularly its calculus concretions, called gall-stones. The author initiated the chapter “Method of Cure” with citations on how gallstone disease was deemed incurable.

Translations of Latin paragraphs by Prof. Iván Salgado, Universidad Nacional Autónoma de México.

- *“So, when yo see jaundiced people being tenacious, healed or relapsing, know for sure that they became ill because of the stone in their gallbladder, hence you must diagnose them as incurable. You will realize this via the autopsies.”*
- *“Gallstones, since they cannot be dissolved, make illness incurable.”*
- *“Since it is hard to diagnose the origin of gallstones from the gallbladder, it is not strange that healing them can be perceived as amazing by most physicians.”*

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# ASPECTS ON INTERVENTIONS IN COMPLICATED GALLSTONE DISEASE

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***To Laura, Leo, Levi and Manar***

***If you don't fail, you're not even trying.***

— Denzel Washington —

# ABSTRACT

**Background:** Laparoscopic cholecystectomy (LC) is the standard treatment for symptomatic gallstone disease. In 10-15% of these patients, common bile duct stones (CBDS) are encountered. These are managed commonly by endoscopic retrograde cholangiopancreatography (ERCP). Rendezvous (RV) intraoperative (IO) ERCP is performed during ongoing cholecystectomy when the cannulation of the bile duct is assisted by a guidewire. When RV ERCP cannot be performed in one session, the so-called RV postoperative (PO) ERCP may be performed.

**Objectives:** 1) To investigate the risk of post-ERCP pancreatitis (PEP) and stone clearance rate in RVIO ERCP for concomitant CBDS during cholecystectomy. 2) To study cholecystectomy rates in Sweden and correlate cholecystectomy rates with the corresponding rates of gallstone complications (GSC). 3) To compare RVIO ERCP with RVPO ERCP in terms of morbidity and stone clearance. 4) To study the risk of gallstone and cholecystectomy related complications if cholecystectomy is scheduled 6 weeks after the initial episode of mild gallstone pancreatitis.

**Methods:** 1) A single center retrospective study of all consecutive IO ERCP procedures between 2000 and 2009. 2) A nationwide registry-based study of all cholecystectomies between 1998 and 2013. Gallstone complications (pancreatitis and cholecystitis) were collected between 1998 and 2013 and indications for cholecystectomy between 2006 and 2013. The age and gender adjusted annual incidences per 100 000 inhabitants were calculated for the Swedish counties. 3) A nationwide registry-based study of all RV ERCP procedures performed for gallstone indications between 2008 and 2014. 4) A single center randomized controlled trial with two parallel arms. Between May 2009 and July 2017, sixty-six patients with mild gallstone pancreatitis were randomized to index cholecystectomy (IC, n=32) or scheduled cholecystectomy (SC, n=34).

**Results:** 1) 307 patients were managed by IO ERCP. When RV cannulation was successful (86%), the PEP risk was 0.4% compared with 14% when conventional cannulation technique was used ( $p < 0.001$ ). Stone clearance was achieved in 88.3%. No mortality occurred within 90 days. 2) A total of 178 441 cholecystectomies were studied. The annual cholecystectomy rates varied widely between the Swedish counties, with a two-fold difference (median 156, range 100 – 207). There was no inverse correlation between the cholecystectomy and GSC rates. 3) A total of 1205 RVIO and 565 RVPO ERCP procedures were retrieved. The RVPO ERCP technique was associated with increased risk for PEP (6.4% vs. 3.2%,  $p=0.003$ ) and postoperative infections (4.4% vs. 2.3%,  $p=0.028$ ) compared with the RVIO ERCP. 4) Gallstone-related complications occurred in nine patients (5 patients with recurrent pancreatitis and 4 patients with biliary colic) in the SC group compared with one patient with pancreatitis in the IC group (26.4% vs. 3.1%,  $p=0.013$ ). Cholecystectomy-related complications occurred in two patients in the SC group compared with one patient in the IC group (7.1% vs. 3.2%,  $p=0.6$ ). Fewer patients were found to have CBDS in the SC group compared with the IC group (10.7% vs. 22.5%,  $p=0.3$ ).

**Conclusions:** RVIO ERCP is feasible and has low risk of PEP. A high rate of cholecystectomy does not seem to protect from gallstone complications. RVIO ERCP is superior to RVPO, both in terms of PEP and postoperative infections. To minimize the risk for additional gallstone-related complications, patients with mild gallstone pancreatitis should undergo cholecystectomy during the first admission.

## LIST OF SCIENTIFIC PAPERS

- I. Noel R, Enochsson L, Swahn F, Löhr M, Nilsson M, Permert J, Arnelo U. **A 10-year study of rendezvous intraoperative endoscopic retrograde cholangiography during cholecystectomy and the risk of post-ERCP pancreatitis.** Surgical Endoscopy. 2013;27(7):2498–503.
- II. Noel R, Arnelo U, Enochsson L, Lundell L, Nilsson M, Sandblom G. **Regional variations in cholecystectomy rates in Sweden: impact on complications of gallstone disease.** Scand J Gastroenterol. 2016;51(4):465–71.
- III. **Intraoperative versus postoperative rendezvous endoscopic retrograde cholangiopancreatography to treat common bile duct stones during cholecystectomy**  
Noel R, Arnelo U, Swahn F  
Submitted
- IV. **The timing of cholecystectomy in mild gallstone pancreatitis: A randomized controlled trial**  
Noel R, Arnelo U, Lundell L, Hammarqvist F, Enochsson L, Sandbom G  
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## LIST OF ABBREVIATIONS

BMI	Body Mass Index
CBD	Common Bile Duct
CBDS	Common Bile Duct Stones
CI	Confidence Interval
ERCP	Endoscopic Retrograde Cholangiopancreatography
ES	Endoscopic Sphincterotomy
GallRiks	Swedish Registry for Gallstone Surgery and ERCP
GSC	Gallstone Complications
ICD	International Classification of Diseases
IOC	Intraoperative Cholangiogram
IOERC	Intraoperative Endoscopic Retrograde Cholangiography
LC	Laparoscopic Cholecystectomy
LCBDE	Laparoscopic Common Bile Duct Exploration
OR	Odds Ratio
PEP	Post-ERCP Pancreatitis
RCT	Randomized Controlled Trial
RV	Rendezvous
RVPO	Rendezvous Postoperative
RVIO	Rendezvous Intraoperative
SF36	Short Form Survey
VAS	Visual Analogue Scale

# 1 GALLSTONE DISEASE

## 1.1 HISTORICAL BACKGROUND:

The first description of the liver and bile duct anatomy probably goes back to the ancient Mesopotamia in Babylon about 2000 years B.C. Liver models made from clay available at the collection of the British Museum in London, clearly illustrate the anatomy of the bile ducts and the gallbladder (**Figure 1**). The first documented gallstones were probably those found in Egyptian mummies presented in the beginning of 1900s in the Museum of the Royal College of Surgeons in London. The mummy's gallbladder was preserved and contained tens of gallstones [Glenn and Grafe 1966; Glenn 1971; Spirou et al. 2013]. In many centuries, the liver was believed to be the center of the soul, the heat and the blood forming organ. Apparently, the lack of the knowledge of the association between gallstones and disease continued for centuries covering the time of the Greek physician, surgeon and philosopher, Aelius Galenus (known as Galen; 129 – 210 A.C.). Alexander Trallianus (525 – 605 A.C.), the famous Greek physician was thought to be the first who described biliary stones in human liver [Thudichum 1863].



*Figure 1. The liver clay model from Mesopotamia.*

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It was not until the sixteenth century before the first reports about gallstones at autopsies were presented by two Italian physicians; the first by Gentile da Foligno in 1341 and later by Antonio Benivieni from Florence in 1506. Galen's teachings continued until the 17<sup>th</sup> century when a revolutionary understanding of physiology of liver and circulation of the heart made a milestone in the history of disease understanding. Many of these new discoveries led to disproving Galen's theories. A more precise description of human gallstones was presented by the anatomist, Andreas Vesalius. He was the first to postulate their associations with diseases [Glenn and Grafe 1966; Bielefeldt 2014]. Another milestone in understanding the association between the stone findings at autopsies and disease were those made by Giovanni Morgagni (1682 – 1771), who is by many considered the father of modern anatomy. Several of the findings he made were patients who suffered from biliary diseases before their deaths. A number of treatises from the 18<sup>th</sup> century on biliary concretions or gallstones describe the chemistry of bile, gallstones formation and symptoms, and signs of gallstone diseases in good details. John Thudichum in his treatise on gallstones from 1863 presents a detailed description of the composition of the gallstones found in the autopsy of a 60 years old lady who died of unknown reasons [Thudichum 1863]. The author describes thread-like fibers of different diameters that could be isolated from the nuclei of these gallstones (**Figure 2**). Cure was mainly non-surgical and focused on dissolution medications, pain relief, and even bloodletting [Coe 1757; White 1777; Thudichum 1863].



**Figure 2.** Gallstones composition by J. Thudichum 1863. Thread-like fibers are biliary casts from nuclei of gallstones.

Acute cholecystitis in antiquity is not well-documented. The condition was probably fatal in many cases. It is believed that Alexander the Great (356-323 B.C.) was thought to die at the age of thirty-three by acute cholecystitis and subsequent peritonitis [Glenn 1971]. Antonio Benivieni (1443 – 1502) performed autopsies in two females who died after having right upper quadrant pain. Although gallstones were found at these autopsies and the liver capsule was clearly diseased, the exact association was not understood [Bielefeldt 2014].

The first surgical intervention made on a gallbladder was the removal of gallstones (cholecystolithotomy) from a stoma on the abdomen that was resulted from a ruptured abscess by the surgeon Joenisius. For nearly two centuries, surgeons focused mainly on techniques for the removal of the gallstones and not the gallbladder. John Bobbs from Indiana in 1867 performed the first cholecystostomy. A breakthrough was the first successful cholecystectomy that was performed and credited to the German surgeon Carl Langenbuch in 1882 [Glenn and Grafe 1966]. A forty-three year old male who was suffering from chronic biliary colic received the surgery and was recovered and discharged later [Traverso 1976]. In 1886, Langenbuch reported 33 gallbladder operations, with a mortality rate of 27% [van Gulik 1986]. Since this time, the number of cholecystectomies increased and by the beginning of the 20<sup>th</sup> century, the operation has rapidly gained popularity. In the era of minimally invasive surgery and introduction of laparoscopic technique, the first laparoscopic cholecystectomy was performed by Erich Mühe in September 1985 in Germany [Litynski 1998] and in Sweden by Dag Arvidsson [Arvidsson et al. 1992].

The first report on visualization of the pancreatic duct by non-operative methods came in 1965 by Rabinov and Simon [Rabinov and Simon 1965]. Later, the process of duodenoscopy, cannulation of the ampulla of Vater, and the opacification of the pancreatic duct was reported by McCune et al in 1968. The ampulla of Vater was described as: “It appears as an elevated red spot on the duodenal mucosa which opens and closes, expelling bile and pancreatic juice” [McCune et al. 1968].

## **1.2 AN OVERVIEW OF GALLSTONE DISEASE:**

Gallstones or biliary lithiasis is the formation of concretions (stones and/or sludge) in the gallbladder (cholecystolithiasis), bile ducts (choledocholithiasis) or both. Gallstone disease is an increasing health problem and is one of the most common gastrointestinal diagnoses. The healthcare costs caused by gallstone disease are about \$6.2 billion per year [Everhart and Ruhl 2009]. Acute gallstone pancreatitis is estimated to result in several thousand hospital admissions in the USA and the UK [da Costa et al. 2016]. In addition, it is important to highlight that costs can also result from a certain surgical practice in treating acute gallstone disease. Deferring the definitive treatment (cholecystectomy) for acute cholecystitis results in considerably increasing the costs [Jones et al. 2012].

## **1.3 EPIDEMIOLOGY OF GALLSTONE DISEASE**

The prevalence of gallstones is about 10-15% of population in western countries with a substantial variation between different ethnic populations and geographical areas [Stinton et al. 2010; Brazzelli et al. 2015]. Whereas exceedingly high rates of gallstone prevalence in some ethnic groups in the Americas are reported, the rates decrease towards the far East. The North American Indians can harbor gallstones in up to 70% [Sampliner et al. 1970; Everhart et al. 2002], the rates in India and Taiwan are between 10 and 20% [Chen et al. 1998; Singh et al. 2001]. Gallstone formation is believed to be influenced by genetic and environmental factors. In the healthy population, epidemiological [Stinton et al. 2010; Xu et al. 2012] and necropsy [Lindström 1977; Attili et al. 1997; Khan et al. 2009] studies have demonstrated a clear increase in the gallstone prevalence with increasing age and female gender. The pathophysiological mechanism behind the predominance in female gender is thought to be hormonal [Stinton and Shaffer 2012]. Several other risk factors have been studied and are presented in the summary **Table 1**. Also, other conditions and diseases have been associated with increased risk of gallstone formation; e.g. hemolytic anemias, diabetes mellitus, metabolic syndrome, liver cirrhosis, and uremia [Chapman et al. 1996; Del Olmo et al. 1997; Borgna-Pignatti et al. 2003; Li Vecchi et al. 2003].

## **1.4 COMMON BILE DUCT STONES:**

Common bile ducts stones (CBDS) or choledocholithiasis is the formation or presence of gallstone in the bile ducts and is estimated to occur in about 10-15 % of patients with gallbladder stones [Li et al. 2011]. Stones result often from migration from the gallbladder, so-called secondary stones, but primary formation may also occur [Ko and Lee 2002]. In the immediate course after cholecystectomy, retained CBDS may be encountered. The prevalence of clinically manifested retained CBDS is reported to be around 2% [Lee et al. 2016].



**Table 1.** Summarized the reported risk factors for gallstone disease

<b>Factors increasing the risk for gallstone disease</b>	
Calorie intake > 8200 J/d	Increases the risk of symptomatic gallstone disease [Maclure et al. 1989]
High BMI and abdominal obesity	Increases the risk in males [Tsai et al. 2004; Festi et al. 2008; Palermo et al. 2013; Shen et al. 2014]
Hereditary	Increases the risk [Attili et al. 2005]
Multiple parities	Increases the risk [Palmero et al. 1982; Gonzalez Villalpando et al. 1997]
High education, high socioeconomic class	Increases the risk [Singh et al. 2001]
<b>Factors decreasing the risk for gallstone disease</b>	
Physical activity	Decreases the risk [Ansari-Moghaddam et al. 2015]
<b>Factors with conflicting effect on the risk for gallstone disease</b>	
Being vegetarian	Probably no effect [Pixley et al. 1985; Pradhan et al. 2009; Walcher et al. 2010]
High Blood lipids	LDL-cholesterol increases the risk [Halldestam et al. 2009], hypertriglyceridemia increases the risk [Sun et al. 2009], and no association demonstrated [Loria et al. 1994]
Coffee consumption	No effect [Walcher et al. 2010], probably protective [Shaffer 2006]. Caffeine may play role to prevent symptomatic gallstone disease [Leitzmann et al. 2002]
Alcohol consumption	No effect [Kratzer et al. 1997], high alcohol consumption (2400g and 1800g/month in males and females) associated with decreased risk of symptomatic gallstone disease [La Vecchia et al. 1994; Katsika et al. 2007]
Smoking	Increased risk [Kono et al. 2002] and no effect [Katsika et al. 2007].

## **1.5 GALLSTONE COMPOSITION:**

The exact mechanism behind the formation of gallstone is not fully understood. One of the pathophysiological step is believed to be the result of an unbalance or supersaturation of bile components foremost cholesterol. The main types of gallstones are; cholesterol, mixed type (cholesterol as main component) and pigment stones (black or brown). Cholesterol stones are light in color and less hard. Pigment stones are darker in color and are normally smaller in size [Sutor and Wooley 1974]. A survey of over a thousand gallstones in Germany revealed that cholesterol is the main substance and was detected in 95% of the gallstones, followed by bilirubin in 30% and calcium in 10% [Schafmayer et al. 2006]. Differences in bile and gallstone composition between western and eastern populations have been shown. Higher cholesterol concentrations were demonstrated in bile obtained from Swedish compared to Japanese patients [Nakayama and van der Linden 1971]. The prevalence of cholesterol stones decreases with increasing age. Pigment stones are more common in lower age groups and in hemolytic diseases [Soloway et al. 1986; Diehl et al. 1995].

## **1.6 NATURAL HISTORY OF GALLSTONE DISEASE**

Studies of the natural history of gallstones with long term follow-up have suggested that symptoms generally develop in about 2-4% of the population per year in the first 10 years [Schwesinger and Diehl 1996]. Furthermore, complications or symptoms were suggested to develop in about 7.6% during a five-year follow-up [Halldestam et al. 2004] and that almost 22% of asymptomatic patients with gallstones will become symptomatic during a period of 8.7 years [Festi et al. 2010]. Even though most patients harboring gallstones are asymptomatic and are believed to remain asymptomatic, at least 12000 cholecystectomies are performed annually in Sweden [Glambek et al. 1989; NIH consensus statement 1992; Enochsson et al. 2013].

Regarding the natural history of common bile duct stones, large controlled studies on this topic are lacking. Prospective studies have shown that the majority of common bile duct stones tend to pass without causing any symptoms [Acosta et al. 1977] or biliary complications such as acute pancreatitis or biliary obstruction [Murison et al. 1993; Collins et al. 2004; Caddy et al. 2005]. In contrast, there is evidence from a large cohort study from Sweden that the natural course of small CBDS detected during cholecystectomy may not be favorable. The study demonstrated higher rates of incomplete stone clearance and/or complications when CBDS smaller than 4mm detected during cholecystectomy were left without any measures compared to patients who received intervention [Möller et al. 2014].

## 1.7 SYMPTOMATOLOGY OF GALLSTONE DISEASE

*Right upper quadrant pain* is the most common presentation of symptomatic gallstone disease. It can radiate to the back or to the epigastrium. This is referred to as *biliary colic* and is the predominant presentation of cholecystolithiasis and accounts for majority of cholecystectomies especially in young females [Pålsson and Sandblom 2015]. Associated symptoms are nausea, vomiting, pain in the right shoulder, and intolerance to fatty food [Festi et al. 1999]. A large population-based epidemiologic study comparing individuals with gallstones and those without has reported that the pain in the epigastrium and even in the right upper quadrant is associated with gallstones. This together with the absence of heartburn and presence of intolerance to fatty or fried food was significantly associated with gallstones [Festi et al. 1995]. Another study has shown no association between right upper quadrant pain and the presence of gallstones [Jørgensen 1989]. For example, it is common for healthy individuals without gallstones to have abdominal symptoms or pain that is similar to the symptoms of individuals that have gallstones [Glambek et al. 1989].

*Jaundice* (also called *icterus*) is the yellow pigmentation of skin, mucous membranes and the sclerae caused by elevated serum bilirubin levels (hyperbilirubinemia). *Obstructive jaundice* is hyperbilirubinemia caused by obstruction of the bile ducts which can result from CBDS. When obstructive jaundice is caused by impacted gallstone at the level of the ampulla of Vater, the condition is commonly accompanied by abdominal pain.

*Abnormal liver function tests:* It is common that patients with gallstones in the CBD present only abnormally elevated liver enzyme tests. In a study of hundred patients with symptomatic CBDS, the elevated levels of gamma glutamyl transpeptidase (GGT) and alkaline phosphatase (ALP) were the most specific abnormal tests [Anciaux et al. 1986].

## 1.8 COMPLICATIONS OF GALLSTONE DISEASE:

When gallstone disease becomes symptomatic, pain is the most dominant symptom occurring in about 90% of patients [Gracie and Ransohoff 1982; Attili et al. 1995]. The risk of developing biliary complications is estimated to be 3% over a 10-year period, as demonstrated in the GRPECO study [Attili et al. 1995].

### **1.8.1 Cholecystitis:**

The pathophysiology behind *acute cholecystitis* is thought to be an obstruction of the bile flow due to stone impacting the infundibulum or cystic duct. Acute cholecystitis is the most common complication of gallstones [Gomes et al. 2017]. Although the diagnosis is mainly based on clinical assessment, this can sometimes be difficult due to the absence a single clinical or laboratory finding of high diagnostic accuracy [Ansaloni et al. 2016]. Patients usually present with right upper quadrant pain and/or signs of systemic inflammation. Local signs include Murphy's sign, which is considered positive when the patient stops breathing as the examiner palpates the right subcostal region and touches the tender and inflamed gallbladder [Aldea et al. 1986]. The Tokyo Guidelines were developed originally in 2006 to assist in the diagnosis and in severity staging of patients with cholecystitis. The guidelines were revised in 2013 [Yokoe et al. 2012, 2013]. These guidelines together with other clinical scoring systems to predict the severity of cholecystitis have not been validated by clinical studies [Ansaloni et al. 2016]. *Chronic cholecystitis*, on the other hand, occurs when repeated and chronic inflammation results in scarring and shrinkage of the gallbladder.

### **1.8.2 Acute gallstone pancreatitis:**

Also, known as biliary pancreatitis is a condition that is characterized by acute inflammation of the pancreas, caused by obstruction of the pancreatic outflow secondary to stone impaction at the ampulla of Vater.

Gallstone pancreatitis is one of the most common causes of pancreatitis in the western world with increasing incidence globally [van Baal et al. 2012; Yadav and Lowenfels 2013]. The disease causes considerable costs and burden on the health care systems in the USA [Kamal et al. 2017]. The diagnosis is made when two out of three criteria are present; acute abdominal pain, elevated serum amylase level 3 times ( $> 3$  microkat/L) above the upper normal limit or evidence of pancreatitis on imaging modality, e.g. tomography (CT) of abdomen. The disease is mild and self-limiting in almost 80% of patients. In the remaining 20% the disease can cause severe inflammation with organ failure and increased mortality [Banks et al. 2006].

The crude incidence of first attack of gallstone pancreatitis in Sweden was estimated by a retrospective study from the city of Malmö to be around 7.3 in men and 10.5 in women per 100 000 and year. In addition, the overall annual incidence of gallstone pancreatitis was shown to increase with increasing age [Appelros and Borgström 1999].

### **1.8.3 Cholangitis:**

Occurs when there is biliary obstruction that is superimposed by secondary bacterial infection. Clinically, cholangitis is characterized by the so-called Charcot triad, consisting of

fever, right upper quadrant abdominal pain, and jaundice [Lipsett and Pitt 1990]. It is however important to emphasize that the classical picture with the Charcot's triad is not always present. Adding hypotension and confusion to the triad occurs in severe cases and is called the pentad of Reynold. Thus, the severity of the condition can vary from self-limiting to life-threatening condition with septic shock and organ failure. Therapy of acute cholangitis includes antibiotics and biliary drainage. Without biliary drainage the mortality of acute cholangitis can reach 100% [Mosler 2011].

#### **1.8.4 Other complications:**

*Mirizzi's syndrome* is a rare condition that develops when the bile duct is obstructed externally by stone impaction in the infundibulum part of the gallbladder or the cystic duct. The condition was first described by the Argentinian surgeon Pablo Mirizzi in 1948, who thought that the condition was caused by functional spasm of the circular muscles of the extrahepatic bile ducts [Beltrán 2012]. *Cholecystoenteric fistula* and subsequent small bowel obstruction can develop as a result of severe acute cholecystitis causing gangrene and perforation of the gallbladder. Stones can then migrate to the bowel through the fistula, and when large enough can cause acute small bowel obstruction known as *gallstone ileus*.

## 1.9 TREATMENT OF GALLSTONE DISEASE

### 1.9.1 Conservative management

When treating patients with gallstones, it is essential to distinguish between patients who have had a complication and those who do not. Due to lack of randomized controlled trials on the natural history of gallstone disease, the available evidence on this topic is based on epidemiological studies [de Reuver et al. 2016] and clinical experience. According to the NIH consensus guidelines, it is generally accepted that asymptomatic patients do not require any surgical treatment [NIH consensus statement 1992; Gollan JL et al. 1993].

### 1.9.2 Surgical Management

*Cholecystectomy* - removal of the gallbladder: is the only established definitive surgical therapy for symptomatic gallstone disease [Gollan JL et al. 1993]. In the advent of minimally invasive surgery, laparoscopic cholecystectomy has become the treatment of choice for symptomatic gallstone disease and is one of the most common surgical operations [Sundbom and Hedberg 2014]. It is normally performed by the four-trocar technique introduced into the abdominal cavity under general anesthesia. Since the introduction in the 1990s, the number of laparoscopic operations on the gallbladder has increased worldwide [Rosenmüller et al. 2007]. Open cholecystectomy is performed when laparoscopic surgery is technically demanding, carries high operative risks or when there is a general contraindication to laparoscopic surgery. In Sweden, the annual number of laparoscopic cholecystectomies has steadily increased and nearly 12 000 cholecystectomies are performed every year [Nilsson et al. 2005; Enochsson et al. 2013; Sundbom and Hedberg 2014].

#### 1.9.2.1 Treatment of cholecystolithiasis

Cholecystectomy is the recommended treatment for symptomatic cholecystolithiasis. This indication, however, covers complicated (cholecystitis) and uncomplicated cholecystolithiasis. Despite the increasing rates of laparoscopic cholecystectomy globally, there is wide variation in the cholecystectomy rates within and between countries [Singh et al. 2001; Everhart et al. 2002]. The explanation is two-fold:

First; there is evidence that the introduction of the “safer” laparoscopic cholecystectomy has contributed to the widening of cholecystectomy indications, so-called reduced surgical threshold for uncomplicated cholecystolithiasis [Steinle et al. 1997; Mallon et al. 2006]. In addition, it is important to emphasize that most cholecystectomies are performed on uncomplicated biliary colic indications [Gurusamy et al. 2013]. Thus, patient selection is subject to a diversity of factors that can result in unjustified cholecystectomies.

Secondly; despite the clear recommendation for early cholecystectomy in acute cholecystitis by randomized studies [Gutt et al. 2013], cholecystectomy is still subject to local surgical

preferences resulting in wide institutional and national variations in the operating rates for acute cholecystitis [Cameron et al. 2004; Yamashita et al. 2006; Germanos et al. 2007]. The persistence of abdominal pain after cholecystectomy (the so-called *post-cholecystectomy syndrome*) can occur in up to 30% of patients [Ros and Zambon 1987]. Women with abdominal pain as the only indication for cholecystectomy were shown to correlate significantly with low gastrointestinal Quality-of-life score [Wanjura et al. 2014]. The introduction of minimally invasive surgery and the increasing awareness and pressure from patients harboring gallstones on healthcare systems have resulted in an increasingly liberal attitude to operate uncomplicated gallbladder stones.

#### *1.9.2.2 Treatment of gallstone pancreatitis*

Although cholecystectomy is recommended for gallstone pancreatitis, international guidelines are not very clear in cases of mild gallstone pancreatitis [van Baal et al. 2012]. The British Society of Gastroenterology and American Gastroenterological Association recommend cholecystectomy within 2 to 4 weeks from the index episode [Working Party of the British Society of Gastroenterology et al. 2005; Tenner et al. 2013; Working Group IAP/APA Acute Pancreatitis Guidelines 2013]. It is also advised in severe gallstone pancreatitis with systemic or local complications to wait until the patient's clinical condition allows performing cholecystectomy. In addition, studies have demonstrated varying degrees of adherence to the international guidelines when it comes to the timing of cholecystectomy [Nguyen et al. 2008; Creedon et al. 2016; Kamal et al. 2017; Ragnarsson et al. 2017]. A systematic review by Van Baal showed that interval cholecystectomy was associated with an overall readmission rate for biliary events in 18% of patients with mild gallstone pancreatitis [van Baal et al. 2012].

#### *1.9.2.3 Treatment of choledocholithiasis*

The choice of the method for the treatment of common bile duct stones (CBDS) is still controversial [Dasari et al. 2013]. In patients with prior cholecystectomy, CBDS are treated exclusively by endoscopic retrograde cholangiopancreatography (ERCP). However, in non-cholecystectomized patients, the choice of the treatment method is dependent on factors such as time relation to cholecystectomy and the availability of surgical expertise. Historically CBDS were treated by open bile duct exploration. However, there has been a shift to more minimally invasive techniques like ERCP, due to the high complication rates and decreasing experience [Livingston and Rege 2005]. Nowadays, ERCP is the most common method worldwide to treat bile duct stones [Strömberg and Nilsson 2011; Reinders et al. 2014].

### 1.9.3 Endoscopic Retrograde Cholangiopancreatography – ERCP

ERCP is an endoscopic investigation of the bile duct and/or pancreatic duct that was introduced in the late 1960s. The very first step in the history of ERCP were in the form of diagnostic attempts to opacify the pancreatic ducts as a workup in the diagnosis of pancreatic diseases. Later, and with the development of the side-viewing flexible duodenoscopy it was possible to cannulate the bile and/or pancreatic ducts [Cotton et al. 1972; Cotton and Leung 2014]. Other milestones in the development of ERCP, are the introduction of therapeutic measures like endoscopic sphincterotomy (ES) and technique for biliary or pancreatic stenting. The wide accepted term “ERCP” was established at a meeting at the World Congress in Mexico City in 1974. ERCP technique has further developed in the last decades with the introduction of additional therapeutic modalities. The introduction of the balloon dilatation, basket stone retrieval, per-oral ERCP-assisted cholangioscopy and intraductal electrohydraulic lithotripsy have all contributed to an increased therapeutic value of ERCP.

ERCP is nowadays considered to be a routine technique to treat common bile duct stones and during the last decades it almost entirely has replaced more invasive techniques [Strömberg and Nilsson 2011; Dasari et al. 2013]. In the context of cholecystectomy, ERCP is commonly performed prior to cholecystectomy. Postoperative ERCP is normally reserved for patients where CBDS are found on the intraoperative cholangiogram (IOC) [Cuschieri 2000].

#### ERCP Complications:

Since its introduction, it has increasingly become clear that ERCP procedure has an invasive nature and thus carries potential risks. The most ERCP-specific and potentially life-threatening condition is the so-called post-ERCP pancreatitis (PEP). It is by far the most feared and common ERCP-specific complication. Other complications that may occur are bowel perforation, bleeding and ascending cholangitis. Mortality of up to 6% have been reported [Cotton et al. 2009; Kalaitzakis 2016]. Another well-known technical issue with ERCP procedure is the cannulation failure, which basically results in procedure failure [Williams et al. 2007].

#### 1.9.3.1 Post-ERCP pancreatitis (PEP):

According to the consensus guidelines by P. Cotton and co-authors, PEP is defined by typical abdominal pain, amylase levels > 3 times upper normal limit more than 24 hour after the procedure and subsequent need for hospitalization or prolonged admission [Cotton et al. 1991b, 2009]. Population-based studies of large number of ERCP procedure have identified several factors that increase the risk of PEP. Risk factors such as female gender, young age, injection of contrast medium into the pancreatic duct (pancreatogram), pancreatic duct instrumentation, pancreatic sphincterotomy, balloon dilatation of an intact sphincter, previous PEP, and the presence of sphincter of Oddi dysfunction (SOD) have been described [Freeman



et al. 2001; Cotton et al. 2009; Freeman 2012]. Additionally, difficult cannulation resulting from technical problems in achieving deep cannulation or entrance into the bile ducts has been reported as a risk factor to increasing the risk for PEP [Cotton et al. 1991b; Halttunen et al. 2014]. Self-expandable biliary metal stent placement was shown to be an independent risk factor to increase the risk of PEP, caused by the mechanical compression of the pancreatic duct [Côté et al. 2010]. Another factor of contradictory impact on the risk of PEP is the caseload of the treating hospital. While Loperfido et al. showed in a large prospective multicenter study that a low caseload was associated with major adverse events after ERCP procedure, the inverse association was demonstrated from Sweden [Loperfido et al. 1998; Enochsson et al. 2010].

The exact pathophysiologic mechanism behind PEP involves a complex multifactorial mechanism. Indeed, trauma to and/or the resulting edema to the ampulla caused by repeated manipulation or diathermy damage after ES, pancreatic duct injury caused by the guidewire passage or irritation by contrast medium are among the reported causative factors [Parekh et al. 2017].

PEP rates were reported by large prospective studies to develop in less than 10% [Loperfido et al. 1998; Freeman et al. 2001; Masci et al. 2001; Bailey et al. 2008]. In Sweden, a nationwide study of 11074 ERCP procedures demonstrated the overall PEP rate to be 5.4% [Enochsson et al. 2010].

#### Prevention of Post-ERCP pancreatitis:

Numerous attempts have been made to prevent PEP or at least minimize the pancreatic injury that can occur following the ERCP procedure. Several methods, pharmacologic and interventional techniques have been reported in literature to prevent or reduce the risk of PEP [Freeman 2016; Parekh et al. 2017]. Non-steroidal anti-inflammatory drugs have been tested with contradicting results. Recently published systematic reviews and meta-analyses have demonstrated a risk reduction for PEP by almost 40% after rectal administration of indomethacin or diclofenac in patients undergoing ERCP [Patai et al. 2017]. Another recent systematic review and meta-analysis has reported a significant reduction in PEP among high-risk patients comparing indomethacin to placebo. The protective effect was not significant in average-risk patients [Inamdar et al. 2017]. Additional chemical protection agents have been studied extensively like protease inhibitors, somatostatin and octreotide, nitroglycerin, allopurinol and *N*-acetylcysteine.

Among the interventional techniques reported to prevent or reduce PEP are the use of guidewire-assisted cannulation technique instead of contrast-assisted technique [Tse et al. 2012], the use of prophylactic pancreatic stents after the ERCP procedure [Ito et al. 2010], and early implementation of the pre-cut sphincterotomy when cannulation attempts by the conventional techniques has failed [Cennamo et al. 2010].

A recent randomized study on the use of endoscopist versus assistant controlled wire-guided cannulation of the bile duct demonstrated a reduction in ERCP complications in the endoscopist-controlled group, mainly due to reduced PEP rate [Buxbaum et al. 2016].

#### *1.9.3.2 Cannulation failure:*

Successful cannulation of the desired duct is the key to accomplish biliary or pancreatic intervention. Difficult cannulation can result in cannulation failure. A prospective study by the Scandinavian Association of Digestive Endoscopy of 907 ERCP procedures has presented a proposal for the term “difficult cannulation”. A difficult cannulation was defined as guidewire cannulation attempts lasting longer than 5 minutes, with 5 attempts or with 2 pancreatic cannulations [Halttunen et al. 2014]. This definition was later adopted by the updated guidelines of the European Society of Gastrointestinal Endoscopy (ESGE) in 2016 [Testoni et al. 2016].

Together with PEP, cannulation failure is perhaps one of the most important quality markers of ERCP and represents one of the most common technical setback that every endoscopist bears in mind. The reported cannulation failure rates can vary considerably. While Williams et al. reported failure rates of 14.4%, a nationwide study from Sweden demonstrated a crude rate of 8% of cannulation failure [Williams et al. 2007; Enochsson et al. 2010].

#### *1.9.3.3 The timing of ERCP in relation to cholecystectomy*

The timing of the ERCP in relation to cholecystectomy is still controversial and various practices are available depending on availability of expertise and management algorithm [Buxbaum 2013]. Principally, ERCP can be performed prior to, during ongoing or after cholecystectomy for patients with suspected or proven CBDS. Patients scheduled for cholecystectomy with biochemical and/or radiological evidence of CBDS, can undergo ERCP prior to the cholecystectomy (preoperative ERCP). This is the most common practice worldwide to treat CBDS [Cuschieri 2000]. ERCP performed after cholecystectomy (postoperative ERCP) is reserved for patients with CBDS discovered during IOC.

Whereas preoperative urgent ERCP is indicated in cholangitis and severe acute gallstone pancreatitis with biliary obstruction [Williams et al. 2017], the decision of elective preoperative ERCP for CBDS is dependent on the availability of ERCP expertise and the probability of having CBDS. The preoperative assessment of the presence of CBDS is based on biochemical testing and/or ultrasonography. Low risk is traditionally assumed if bile ducts are of normal caliber on ultrasonography and liver enzymes are normal. This translates into a chance of having CBDS in 2-5% [Changchien et al. 1995].

There is also evidence that a considerable proportion of patients (up to 55%) have negative finding on ERCP performed prior to cholecystectomy [Cotton et al. 1991a; Alkhaffaf et al.

2011; Reinders et al. 2014]. Preoperative ERCP, in a case-control study, was associated with increased severity of the subsequent laparoscopic cholecystectomy [Ahn et al. 2015]. Undoubtable, when ERCP causes morbidity in up to 10% postoperatively [Enochsson et al. 2010] and mortality in up to 6 % [Cotton et al. 2009; Kalaitzakis 2016], together with the potentially high proportion of negative findings, should preoperative ERCP be considered unnecessary.

Postoperative ERCP carries on the other hand the risk of unpredicted failure, and the need for repeated ERCP attempt or surgery to clear CBDS [Reinders et al. 2014]. This risk is avoided when performing preoperative ERCP as a preoperative ERCP failure may be considered when performing the cholecystectomy.

#### **1.9.4 Rendezvous ERCP (guidewire assisted cannulation):**

By the introduction of the so-called rendezvous (RV) ERCP, a new era in the management of concomitant CBDS during cholecystectomy was entered. The technique was first described by Deslandres et al. in 1992 who reported the feasibility of the technique in 4 patients [Deslandres et al. 1993]. The technique can be performed during ongoing or after cholecystectomy.

##### *1.9.4.1 Rendezvous Intraoperative ERCP – RVIO ERCP:*

The initial reports described a technique that was first introduced during ongoing cholecystectomy for CBDS detected at IOC. Since its introduction, different names have been used to refer to the technique. Intraoperative rendezvous ERCP (RVIO) is perhaps the most common term, but laparoendoscopic technique and single session rendezvous ERCP have also been used.

The cannulation of the CBD is facilitated by an antegrade guidewire that is placed laparoscopically by the surgeon. A more convenient way of introducing the guidewire, is to let it pass through the cholangiography catheter, passing through the cystic duct, the CBD and into the duodenum passing through the ampulla of Vater. In the duodenum, the guidewire is simultaneously caught by a polypectomy snare and pulled through the working channel of the duodenoscope. With the guidewire at hand, the sphincterotome is gently introduced and the bile duct is subsequently cannulated over the very same guidewire. In this manner, selective cannulation of the biliary duct is always achieved and subsequent biliary therapy can be conducted, **Figure 3**.



Since its introduction, the technique has gained popularity and several case-series have been published. A number of advantages of the technique have been reported. One of the most important advantages of the technique is the reduction in the risk for complications especially PEP [Deslandres et al. 1993; Tricarico et al. 2002; Enochsson et al. 2004; Lella et al. 2006; Rabago et al. 2006; La Greca et al. 2007; Swahn et al. 2013a, 2013b]. The obtained selective biliary cannulation at first touch during the ERCP and avoidance of pancreatic cannulation is the main theoretic explanation behind this causality. Additional reported advantages are shortened hospital stay [Basso et al. 1999; Filauro et al. 2000; Iodice et al. 2001; Meyer et al. 2002; Tricarico et al. 2002; Williams and Vellacott 2002; Enochsson et al. 2004; Lella et al. 2006; Morino et al. 2006; La Greca et al. 2007; Tzovaras et al. 2012], single anesthetic session [Deslandres et al. 1993; Cemachovic et al. 2000; Filauro et al. 2000; Meyer et al. 2002; Williams and Vellacott 2002; Wright et al. 2002; Saccomani et al. 2005; Hong et al. 2006; Morino et al. 2006; La Greca et al. 2007], reduced costs [Filauro et al. 2000; Iodice et al. 2001; Saccomani et al. 2005; Morino et al. 2006; Rabago et al. 2006; Garbarini et al. 2017], and high success rates [Filauro et al. 2000; Lella et al. 2006; Morino et al. 2006; Rabago et al. 2006; La Greca et al. 2007, 2017].

However, several drawbacks of the technique have also been reported. Among these, are logistical problems [Meyer et al. 2002; Tricarico et al. 2002; Williams and Vellacott 2002; Wright et al. 2002; Enochsson et al. 2004; Saccomani et al. 2005; Lella et al. 2006; Morino et al. 2006; La Greca et al. 2007] and prolonged cholecystectomy time [Iodice et al. 2001; Meyer et al. 2002; Tricarico et al. 2002; Wright et al. 2002; Enochsson et al. 2004; Saccomani et al. 2005; Lella et al. 2006]. Technical difficulties when passing the guidewire also have been reported [Tricarico et al. 2002; Morino et al. 2006].

The new guidelines from the European Society of Gastrointestinal Endoscopy suggests intraoperative ERCP with laparoendoscopic rendezvous in patients with CBDS who are scheduled for elective cholecystectomy [Testoni et al. 2016].

A meta-analysis by Huang et al., comparing the rendezvous technique to the sequential treatment (usually LC and postoperative ERCP) concluded equal efficacy in terms of stone clearance rates. The difference was mainly due to a lower postoperative complication rates including pancreatitis in the rendezvous group [Huang et al. 2015]. Other systematic reviews and meta-analyses of randomized trials comparing the preoperative ERCP followed by LC with the single-step intraoperative RV ERCP demonstrated similar results, a reduced risk of PEP and overall morbidity in the intraoperative group [Gurusamy et al. 2011; Arezzo et al. 2013; Wang et al. 2013; Tan et al. 2017]. **Figure 4** illustrates the setup of the rendezvous technique in the operating room.



**Figure 4.** The setup and positioning of the equipment of the rendezvous intraoperative technique in the operating room. a) surgeon. b) endoscopist. c) fluoroscopy arm. d) endoscopy equipment and monitor. e) additional endoscopy monitor. f) fluoroscopy monitor. g) anesthesia equipment. h) suction. i) diathermy apparatus. j) ERCP assistant. Photo: Rozh Noel, operating room at Södertälje Hospital.

#### 1.9.4.2 Modifications of the “Rendezvous” Technique:

1. Intraoperative ERCP without routine or with selective guidewire usage. There are descriptions of rendezvous technique without or with selective transcystic guidewire placement. Authors have either omitted the guidewire [Basso et al. 1999; Cemachovic et al. 2000; Kalimi et al. 2000; Iodice et al. 2001; Meyer et al. 2002; Williams and Vellacott 2002; Wright et al. 2002; Wei et al. 2003; Hong et al. 2006; ElGeidie et al. 2011] or used it selectively only when cannulation was difficult [Tatulli and Cuttitta 2000; La Greca et al. 2007]. However, the Karolinska group and several other authors agree on the crucial idea behind using the guidewire to facilitate selective cannulation of the bile duct and minimize pancreatic trauma [Miscusi et al. 1997; Cavina et al. 1998; Iodice et al. 2001; Tricarico et al. 2002; Enochsson et al. 2004; Saccomani et al. 2005; Morino et al. 2006]. This technique has also been called “rendezvous” despite the variation in the guidewire usage.

2. Basso et al. used a transcystic 6F Fogarty balloon catheter for the IOC. When cannulation of CBD was difficult the balloon catheter was pushed into the duodenum and the sphincter of Oddi was dilated. The balloon was withdrawn upwards guiding the endoscopist to obtain cannulation of the bile ducts [Basso et al. 1999].
3. Tatulli et al. used a guidewire inserted transcystically. They used a front-viewing endoscope to pull the guide all the way through the patient's mouth. A sphincterotome was inserted over the guidewire into the working channel of the endoscope [Tatulli and Cuttitta 2000].
4. A modified rendezvous model was adopted by Liu et al. A Dormia basket inserted through the cystic duct was used to pull the guidewire introduced by the duodenoscope. The sphincterotome was then advanced into the bile duct [Liu et al. 2014a, 2014b].
5. Postoperative Rendezvous ERCP - A delayed rendezvous approach by placing a guidewire to be used during a postoperative ERCP. The technique is explained in the next section.
6. Insertion of a biliary stent during cholecystectomy through the cystic duct down to the CBD and out into the duodenum through the ampulla of Vater. Postoperative ERCP is performed within days and cannulation of the bile ducts is assisted by the biliary stent. This technique is practiced in only a couple of Swedish hospitals and outcomes of this technique are essentially unknown.
7. Laparoscopic antegrade sphincterotomy: was first described by DePaula et al. and Curet et al. It implies the insertion of a sphincterotome via the cystic duct through the papilla into the duodenum. A gastroscope is needed to see the sphincterotome in the duodenum. The authors treated 42 patients with choledocholithiasis during cholecystectomy. No major complications or mortality were reported [DePaula et al. 1993; Curet et al. 1995].

#### *1.9.4.3 Rendezvous postoperative ERCP:*

A modified approach to the regular RV ERCP was reported in 1995 by Fitzgibbons et al., who used the technique to treat CBDS during cholecystectomy [Fitzgibbons et al. 1995]. They used a urethral catheter left in the CBD and duodenum when CBDS were discovered by the IOC. Secondary cholangiography was undertaken at the 10<sup>th</sup> postoperative day. If stones were found, the catheter was used to insert a guidewire to the duodenum to assist cannulation of the bile ducts. Due to difficulties in performing the intraoperative RV technique in the same session as the cholecystectomy, several Swedish hospitals have introduced the

rendezvous postoperative (RVPO) technique. This implies the passage and placement of a transcystic guidewire in the same manner as the rendezvous intraoperative ERCP when CBDS are detected by IOC during cholecystectomy. The difference is that the guidewire is held in place in the cystic duct by laparoscopic clips on the cystic stump and the cholecystectomy is finished. The exterior part of the guidewire is kept in place by sterile dressing. The ERCP is then performed as soon as possible within a day or two with full advantage of the guidewire.

### **1.9.5 Surgical treatment of common bile duct stones:**

Common bile duct stones may be removed by open or laparoscopic surgery. The techniques used are transcystic stone extraction, laparoscopic or open common bile duct exploration. Generally, the choice of the technique to manage common bile duct stones is subject to several factors such as the availability of local expertise. However, the advantages of minimally invasive surgery such as laparoscopic cholecystectomy, has imposed increased demands to achieve similar results of treating common bile duct stones.

Several randomized studies have compared the surgical approach to endoscopic. Below is a summary of the surgical techniques:

1. Laparoscopic common bile duct exploration (LCBDE): is the technique where common bile duct stones can be removed through the cystic duct (transcystic – TC) or through the bile duct (transductal -TD). This can be performed simultaneously with laparoscopic cholecystectomy in a single session procedure. The techniques used in the TC approach include either stone extraction by the means of a choledochoscope or stone retrieval by balloon or basket catheters [Lyass and Phillips 2006].

Several case-series have reported the feasibility and safety of the TC LCBDE approach compared to the TD approach. There are however limitations to the technique, represented by the cystic duct anatomy and the number, size, and location of the CBDS. In addition, the technique has a considerable long learning curve estimated to about 250 patients [Zhu et al. 2015].

A systematic review of randomized controlled trials comparing the combined endoscopic/laparoscopic approach with single stage LCBDE demonstrated similar stone clearance rates. However, the TD LCBDE approach had higher complication rates compared to the endoscopic and TC approaches [Reinders et al. 2014].

2. Open common bile duct exploration: access to the CBD can be achieved as in laparoscopic surgery, either by the transcystic approach or by choledochotomy. The transcystic path is preferred as there is no need to T-tube insertion or incision of the CBD. Several techniques to remove the CBDS can be used like flushing with saline, balloon or basket extraction under fluoroscopy.



Open choledochotomy is performed when CBD stones can not be extracted through the cystic duct approach. Whereas this technique predominated for decades, the management of CBDS has changed since the introduction of minimally invasive techniques like ERCP and laparoscopic cholecystectomy. Strömberg et al. demonstrated a gradual reduction in the use of open choledochotomy in Sweden between 1965 and 2009 [Strömberg and Nilsson 2011]. Today, open choledochotomy is rarely performed. The technique involves the use of a T-tube that is left in the CBD where cholangiography is normally performed before the T-tube is drawn.

McSherry et al. reported mortality after choledochotomy combined with cholecystectomy to be 4% [McSherry 1993]. Bile leakage, retained common bile duct stones and cholangitis are among the early complications. Late complications include abscess formation, stricture of the CBD and recurrent CBDS.

## 2 AIMS

- I. To investigate complication rates, foremost PEP rate and stone clearance rate associated with rendezvous intraoperative (RVIO) endoscopic retrograde cholangiopancreatography (ERCP) for common bile duct stones detected during cholecystectomy.
- II. To study the regional differences in cholecystectomy rates in Sweden and how this affects the incidence of gallstone complications.
- III. To compare the single-session rendezvous intraoperative ERCP (RVIO) with the rendezvous postoperative ERCP (RVPO) regarding morbidity in terms of post-ERCP pancreatitis and postoperative infections, and stone clearance.
- IV. To study the outcomes in terms of gallstone and cholecystectomy-related complications if cholecystectomy is scheduled 6 weeks from the initial episode of mild gallstone pancreatitis compared to index cholecystectomy.

## 3 METHODS

### 3.1 PAPER I

#### 3.1.1 Study design and data collection:

The study was designed as a retrospective single-center study of the rendezvous intraoperative endoscopic retrograde cholangiopancreatography (RV IOERC). To address the study hypothesis, all consecutive patients who underwent intraoperative ERCP for concomitant choledocholithiasis during cholecystectomy between January 2000 and December 2009 at the Karolinska University Hospital were included. Patients were identified from the local hospital registry and ERCP and clinical records were studied. Patients with other indications for IOERC during cholecystectomy other than choledocholithiasis (malignancy, bile leakage, unclear anatomy) were excluded.

#### *Study outcome and variables:*

The primary outcome was PEP. Secondary outcomes were stone clearance and mortality. Other registered variables were patients' demographic characteristics and other ERCP complications. PEP was defined according to the criteria proposed by Cotton et al., as typical abdominal pain, amylase level > 3 times the upper normal limit at more than 24 hours after the procedure, and the need for hospitalization or prolonged admission [Cotton et al. 2009].

#### 3.1.2 Statistical analyses:

The data obtained was explored and analyzed by descriptive statistics. The Pearson's Chi-square test was used to compare frequencies for the outcome variable. Statistical significance was set to  $p\text{-value} < 0.05$ .

#### 3.1.3 The rendezvous technique:

IOC was attempted in all patients. When filling defects, stones and/or obstruction of contrast medium to the duodenum were encountered, the decision to perform IOERC was made. The IOC was interpreted by a radiologist and an experienced endoscopist. The equipment in the operating room was arranged according to **Figure 4**. In the meanwhile, the surgeon passed a guidewire (260cm or 450cm, 0.025" or 0.035" guidewire) through the cholangiography catheter into the duodenum. The duodenoscope was pushed into the papillary region and a snare was used to catch the guidewire. Sphincterotomy was performed after a sphincterotome was introduced over the guidewire. The stone extraction was subsequently performed systematically starting at the cystic duct and then the distal CBD. Later, the guidewire was pulled by the endoscopist towards duodenoscope, and then placed deeply in the hepatic ducts. The stone extraction was then continued from the hepatic ducts towards the ampulla. In the case of large or multiple stones or when uncertainty existed a plastic stent was inserted and the patient was scheduled for another ERCP within 6-8 weeks. If passing the guidewire into the duodenum was unsuccessful due to technical difficulties or stone impaction, IOERC was

performed using conventional cannulation technique. This RV technique has been used at the Karolinska University Hospital since 1999.

## **3.2 PAPER II**

### **3.2.1 Study design and data collection:**

The study was conducted as a population-based nationwide registry study. Data was retrieved from two sources: the Swedish National Inpatient Registry (IPR) and the Swedish Registry for Gallstone Surgery and ERCP (GallRiks).

#### *Study outcomes and variables:*

The primary outcome was the regional variation in the annual cholecystectomy rates in Sweden. To study the possible preventive effect of cholecystectomy on gallstone complications (GSC), i.e. gallstone-related cholecystitis and pancreatitis, the cholecystectomy rates for the Swedish counties were correlated with the corresponding rates for GSC.

All cholecystectomies between 1998 and 2013 were obtained for each Swedish county. The rate of the cholecystectomies for each gender and age-group (5-year intervals) between 15 and 84 years was calculated. Similarly, admissions for pancreatitis (ICD code - K85) and cholecystitis (ICD code – K81) were used to obtain information about GSC.

The indications for cholecystectomies obtained from GallRiks between 2006 and 2013, were used as a proxy for GSC; gallstone pancreatitis and cholecystitis. Data about the uncomplicated biliary colic was also obtained from GallRiks. For each of these variables, age- and gender-adjusted rates were calculated for the Swedish counties. All rates are calculated per 100 000 inhabitants and year.

To study eventual impact of the changing cholecystectomy rates over time, the slope of the trend-line ( $\beta$ -value) for each county was calculated and was used in subsequent analysis.

### **3.2.2 Statistical analyses:**

Descriptive statistics were applied. Linear regression model was used to correlate the annual cholecystectomy rates and the annual rates for GSC. A  $p$ -value  $< 0.05$  was considered statistically significant. With a correlation coefficient of 0.25, the study would have a statistical power of 80% to detect a statistically significant correlation at the  $p < 0.05$  level.

### **3.2.3 The Swedish National Inpatient Registry (IPR):**

The IPR, also called the Hospital Discharge Registry (Swedish: slutenvårdsregistret), is part of the National Patient Registry (Swedish: patientregistret) where inpatient data are prospectively registered. The registry was launched in 1964 by the National Board of Health and Welfare (formerly known as Medicinalstyrelsen and since 1968, Socialstyrelsen). The coverage has gradually increased since its start and has essentially complete national coverage from 1987. Currently more than 99% of all somatic and psychiatric hospital discharges are registered in the IPR. The variables registered in the IPR include patient-related data, data provided by the caregiver, administrative data and medical data. Information about admission of individual patients, including diagnosis, operations and discharge codes are registered. The diagnosis in IPR uses codes according to the World Health Organization (WHO) International Classification of Diseases (ICD). The IPR is regarded as a major source of data in clinical research, and it can be cross-matched with other high-quality registries like the Swedish Cancer Register and the Cause of Death Register. Every Swedish resident is assigned a unique personal identification number, a 10-digit number consisting of the combined date of birth and 4 additional digits. This unique number is registered across all the quality registries in Sweden and allows cross-matching between these [Ludvigsson et al. 2011].

### **3.2.4 The Swedish Registry for Gallstone disease and ERCP (GallRiks):**

The National Quality Registry for Gallstone disease and ERCP (GallRiks - <http://www.ucr.uu.se/gallriks/>) officially started in 1<sup>st</sup> May 2005 in order to meet the need for a high-quality tool that could facilitate improvement in the care of patients with gallstone disease and the need for national research platform for these patients. A working group was setup by the Swedish Surgical Society in the spring of 2005. A list of relevant demographic and clinical variables was selected to be included in each record and the Uppsala Clinical Research Center – UCR was chosen as the administrative domain. To enable a flexible registration, GallRiks uses a web-based questionnaire accessible to all Swedish hospitals and clinics performing gallstone surgery and ERCP. The GallRiks utilizes full flexible platform where clinic-specific or new national variables can be added. The registry includes information about ERCP procedures performed irrespective of indications. Patient and procedure-related data (cholecystectomy and ERCP procedures) are prospectively registered. Procedure-related complications are registered at a 30-day interval.

#### *Coverage and validity:*

The number of surgical units connected to GallRiks has increased from 26 in 2005 to full national coverage with 72 units in 2011 [Enochsson et al. 2013]. The number of cholecystectomies registered in the GallRiks has increased since 2007 and in 2011 covers more than 80% of all cholecystectomies in Sweden [Rystedt et al. 2014]. A 30-day complication registration is estimated to be completed in at least 95% of the registered

cholecystectomies and ERCPs. GallRiks is continuously validated by an independent external reviewer of all participating hospitals. This is achieved by comparing randomly selected records from GallRiks at each hospital with the medical records. Results of national coverage and validation process are published in annual reports [Enochsson et al. 2013; Rystedt et al. 2014]. Several studies with high clinical impact on the management and care of gallstone disease have been published with data derived from GallRiks [Enochsson et al. 2015].

### 3.3 PAPER III

#### 3.3.1 Study design and data collection:

This study was designed as a population-based nationwide registry study. The study aimed at comparing morbidity rates between two groups of patients who received rendezvous ERCP for concomitant CBDS during cholecystectomy. The groups were:

- a) Patients who received ERCP by the single-session RV intraoperative (RVIO) technique.
- b) Patients treated by the RV postoperative (RVPO) technique.

To achieve this, the GallRiks was searched for patients who underwent ERCP for gallstone indications (gallstone pancreatitis, common bile duct stones and cholangitis) between 2008 and 2014. The search results were further refined by including patients who also had a cholecystectomy performed within 30 days before or after the ERCP procedure.

Each ERCP procedure is registered in GallRiks with a variable called “Rendezvous”. This enabled further refinement of above search results to include only ERCP procedures performed by the RV technique.

#### *Study outcomes and variables:*

The primary outcome variables were PEP and postoperative infection rates. Secondary outcome was the stone clearance rate. Demographic and procedure-related data were obtained. Complications to the ERCP and cholecystectomy procedures at 30-day interval were extracted. **Table 2**, shows the variables used in this study.

PEP in GallRiks is defined according to Cotton et al. [Cotton et al. 2009], as typical abdominal pain, amylase level > 3 times the upper normal limit at more than 24 hours after the procedure, and the need for hospitalization or prolonged admission. Surgical site infections and deep abscesses, but not cholangitis, were considered postoperative infections.

### 3.3.2 Statistical analyses:

Continuous variables are presented either as means with standard deviations (normally distributed) or as medians and range (not normally distributed). Categorical variables are presented as frequencies. To compare categorical variables, Pearson Chi-square test was used, otherwise Fischer's exact test in case of small frequencies. Two-sided *t*-test was used to compare the means of two continuous variables. The Mann-Whitney U test was used to compare continuous variables not normally distributed. *P*-values < 0.05 were considered statistically significant.

#### *Multivariate analysis:*

Because the primary outcomes can be affected by several confounding factors, a multivariate logistic regression model was setup to analyze association between the rendezvous technique and the primary outcome variables. Clinically relevant factors that might have impact on the outcome variable were used in the model. The results are presented as odds ratios (ORs) with their 95% confidence intervals (CIs).

Two models are presented:

- a) PEP multivariate model was adjusted for confounding factors including age, gender, duration of the ERCP procedure, center- and endoscopists volumes, pancreatic duct cannulation, and the cannulation technique used (over- or beside-the-guidewire).
- b) Multivariate model for postoperative infections was adjusted for age, gender, antibiotic usage, hospital stay, postoperative bleeding, duration of cholecystectomy, and postoperative bile leakage.

These factors were included in the model separately and subsequently removed if the model was unchanged. The statistical analyses were performed using Revolution Analytics (Version 0.99.863 – © 2009-2016 RStudio, Inc.).

**Table 2.** *The variables used in paper III*

<b>Demographic variables</b>	Age and gender.
<b>Outcome variables</b>	Primary - PEP and postoperative infections rates.  Secondary - stone clearance rates.
<b>ERCP-related variables</b>	Procedure time (min), the RV technique (RVIO/RVPO), pancreatic duct cannulation (yes/no), cannulation technique (beside-/over-the-guide-wire), endoscopist-volume (high > 200, low < 200 procedures), hospital caseload (low, intermediate and high).
<b>Cholecystectomy-related variables</b>	Procedure time (min), use of antibiotics (prophylaxis/therapy).
<b>Other variables</b>	Days between cholecystectomy and ERCP, Days between ERCP and discharge.
<b>Other complication variables</b>	Retained stones, cholangitis, thromboembolism, bleeding, bile leakage, and perforation.



### **3.4 PAPER IV**

#### **3.4.1 Study design:**

This study was designed as a single-center randomized controlled trial with two parallel arms. According to international guidelines, cholecystectomy is the definitive treatment for mild gallstone pancreatitis, and is recommended within 2-4 weeks from the initial (index) admission. There is an increased, however, a risk for recurrent pancreatitis and other biliary adverse events in patients while waiting for cholecystectomy. To study the risk for gallstone- and cholecystectomy-related complications, patients with mild gallstone pancreatitis were randomized into two groups:

1. Index Cholecystectomy (IC): the group who received the intervention (cholecystectomy) during the same admission for gallstone pancreatitis. The cholecystectomy was performed within 48 hours after randomization.
2. Scheduled Cholecystectomy (SC): the group who was discharged and scheduled for cholecystectomy after 6 weeks from randomization.

#### *Eligibility and inclusion criteria:*

Patients aged between 18 and 80 years, with gallstone pancreatitis admitted to the Karolinska University Hospital between May 2009 and July 2017 were eligible for inclusion. The pancreatitis diagnosis was affirmed when two out of three criteria were present; acute abdominal pain, elevated serum amylase level 3 times ( $> 3$  microkat/L) above the upper normal limit or evidence of pancreatitis on imaging modality, e.g. tomography (CT) of the abdomen. The gallstone etiology was confirmed by abdominal ultrasonography with evidence of 1 or more gallstones or sludge in the gallbladder and/or in the bile ducts. That the disease was of a mild degree was assessed by the following:

1. C-reactive protein at randomization less than 150 mg/L and a rapidly improving clinical course [Werner et al. 2003].
2. Absence of organ failure (more than 48 hours) and local complications [Bradley 1993].

#### *Exclusion criteria:*

1. Alcohol induced pancreatitis.
2. Pancreatitis with organ failure.
3. Patients with concurrent cholangitis or cholestasis requiring intervention.
4. Pregnancy.

#### **3.4.2 Randomization:**

Verbal and written information were provided. Following a written consent, the patients were randomized to index cholecystectomy (IC) or scheduled cholecystectomy (SC) using a sealed envelope. No block randomization was done. Blinding was not possible due to the nature of the study.

### **3.4.3 Study variables and outcomes:**

The primary outcome was gallstone-related complications in terms of recurrent gallstone pancreatitis, cholangitis, or cholecystitis within 6 weeks or until scheduled cholecystectomy. Secondary outcomes were cholecystectomy-related complications within 1 month from surgery, the number of patients with CBDS at cholecystectomy requiring ERCP and patients-reported quality-of-life and pain. The studied variables were extracted from the clinical notes.

### **3.4.4 The Short Form Survey (SF-36) and pain questionnaires:**

Patients included in this study reported their pain and quality of life through pain questionnaires (Visual Analogue Scale) and the Short Form survey (SF36) at randomization and after one month.

SF-36 is a validated form for subjective assessment of health consisting of 36 simple items. It is commonly used as an outcome measure in clinical trials. The questions in the survey gives information around three important aspects of health; functional status, well-being and general health. Normally, the scores in these questions are transformed into 8 health-related aspects: physical functioning, role limitations due to physical health, role limitations due to emotional health, energy/fatigue, emotional well-being, social functioning, pain and general health [Ware and Sherbourne 1992; Jenkinson et al. 1994].

### **3.4.5 Statistical analyses:**

Based on the assumption that IC will reduce the risk of gallstone-related events from 40% to 10%, a total sample size of 32 in each group would be needed to reach a statistical power of 80% to detect a significant difference at the  $p < 0.05$  level. To compensate for drop-outs a total sample size of 70 was stipulated.

Numeric variables are presented as means and standard deviations (SD). Median and range was used if variables were not normally distributed. Numeric variables were analyzed with the Student's t-test. Frequencies were compared by the Chi-square test or Fisher's exact test. The Mann-Whitney U test was used to test differences between not normally distributed numeric variables. Intention-to-treat analysis was used. A statistical significance level of  $P < 0.05$  was used in this study. Statistical analyses were performed using Revolution Analytics (Version 0.99.863 – © 2009-2017 RStudio, Inc.).

#### *Ethical consideration:*

The regional ethical committee for Stockholm county approved the study (approval ID: 2008/1030-31/3). Due to the study's nature, with the potential increased risk for recurrent pancreatitis in the SC – group an independent Safety Committee was established to monitor the study participant for unintentional risks that may have arisen because of randomization. The safety committee was established in 2010 and the final report was presented in 2017. The study was registered in clinicaltrials.gov (ID: NCT02630433)

#### **3.4.6 The cholecystectomy and ERCP-procedures:**

Cholecystectomy was performed with a standard 4-trocar laparoscopic technique. Standard pre-, intra- and postoperative care was provided. Prophylactic antibiotics were not used routinely during the cholecystectomy procedures unless intraoperative ERCP was performed for CBDS discovered on the IOC. In that case, a single dose of 4g Piperacillin/Tazobactam was given intravenously before the start of the ERCP. In case of penicillin allergy, one dose of Ciprofloxacin 500mg intravenously was given instead.

Pre-cholecystectomy ERCP is normally not practiced for CBDS stones at the Karolinska University Hospital. Transient elevated LFTs were considered as stone passage and patients were included. Any signs of persistent cholestasis or acute cholangitis resulted in exclusion and an ERCP was performed.

## 4 RESULTS

### 4.1 PAPER I:

#### 4.1.1 Patient characteristics:

During the study period, a total of 2635 laparoscopic and 354 open cholecystectomies for gallstone indications were performed. Of the 330 patients who were treated by IOERC, 307 patients had CBDS, 208 females and 99 males with mean age of 48.5 years (range 13-93 years). Hence, the prevalence of CBDS detected during cholecystectomy was 10.2%.

#### 4.1.2 Rendezvous cannulation:

Passing the guidewire through the cystic duct to the duodenum was attempted in all patients. However, this was successful in only 264 patients (86%). Thus, conventional cannulation technique was used in the remaining 43 patients.

#### 4.1.3 Post-ERCP pancreatitis:

PEP occurred in one patient when RV cannulation was performed compared with six patients cannulated by the conventional technique (0.4% vs. 14%,  $p < 0.001$ ). The overall PEP rate was 2.3%. Two patients developed severe PEP, requiring admission at the intensive care unit.

#### 4.1.4 Stone clearance:

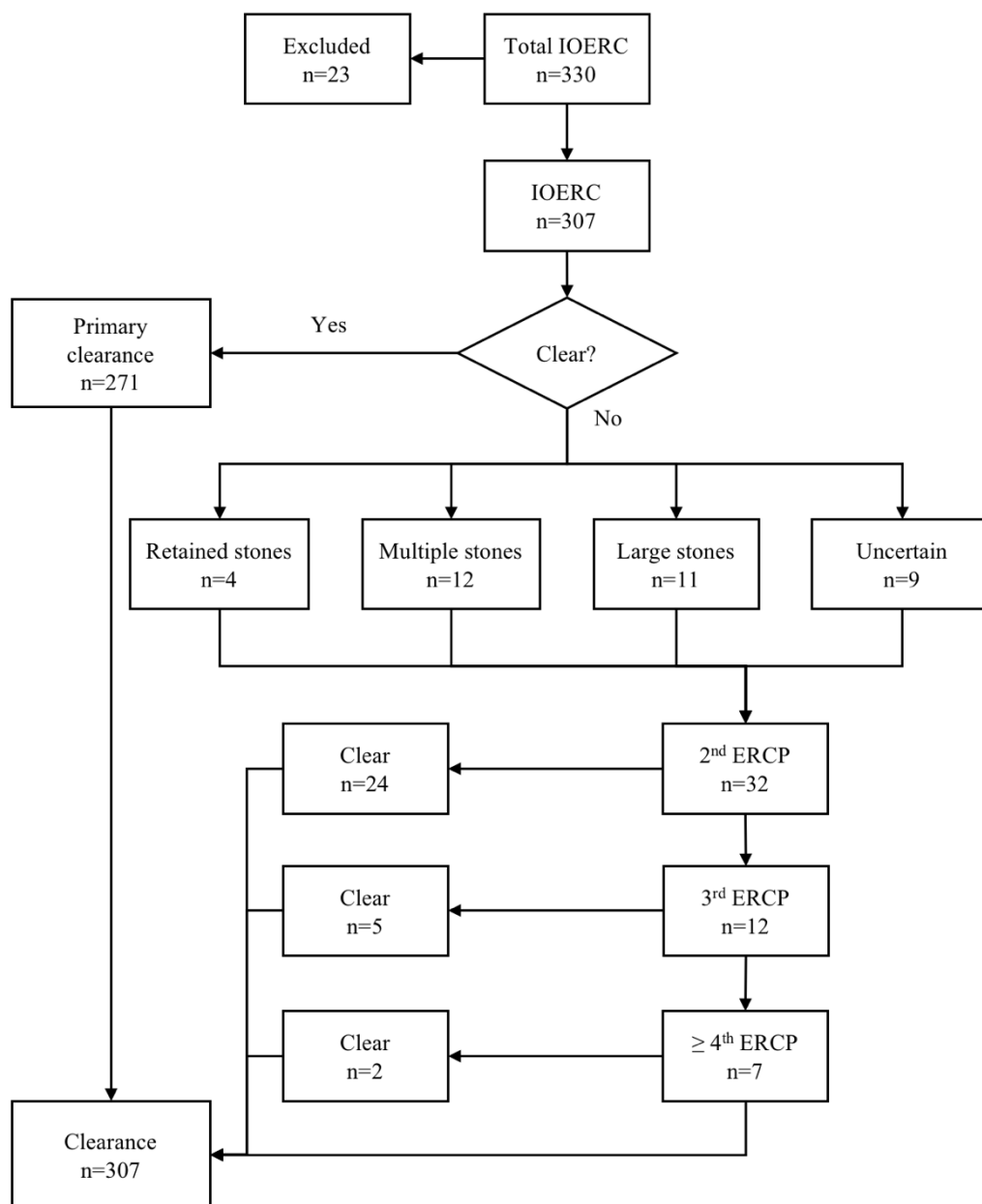
Stone clearance was achieved in 88.3% of patients by the first IOERC session. Repeated ERCP sessions were required in 36 patients (11.7%). Of these, four patients (1.3%) due to retained stones and thirty-two patients (10.4%) due to multiple or large stones, or uncertain stone clearance. All patients were finally cleared by successive ERCP sessions (**Figure 5**).

#### 4.1.5 Miscellaneous results:

The median hospital stay was 2 days (mean 2.5 days). 63.4% of the procedures were performed on urgent basis. While 90.6% of cholecystectomies were completed laparoscopically, 3.6% were started as open surgery and 5.9% were converted. Median operative time including ERCP time was 186 minutes (mean of 198 min). One retroperitoneal perforation occurred that was managed conservatively. No bleeding requiring intervention occurred. No mortality occurred within 90 days.

#### 4.1.6 Trends:

The annual number of patients treated by RV IOERC technique increased during the study period from 18 in 2000 to 41 in 2009. While the operation time including ERCP time remained stable during the study period, the percentage of the patients that were cleared at the first ERCP dropped in the last years.



**Figure 5.** The flowchart of the patients treated by intraoperative ERCP (IOERC).

#### **4.1.7 Comments:**

The main finding of the study was the significantly reduced PEP rate (0.4% vs. 14%,  $p<0.001$ ) when rendezvous cannulation was successful compared with conventional cannulation during the intraoperative ERCP when CBDS were detected during cholecystectomy. This result is in line with many previously published case-series that reported low PEP rates [Iodice et al. 2001; Saccomani et al. 2005; Lella et al. 2006; Gagner 2008]. Despite the feasibility of the rendezvous intraoperative ERCP as demonstrated by the study, obstacles in performing the rendezvous ERCP such as passing the guidewire were also presented. Such a difficulty can jeopardize the rendezvous ERCP. In this study, only 86% of the patients were cannulated by the rendezvous technique, leaving the remaining patients to undergo intraoperative ERCP with conventional cannulation technique.

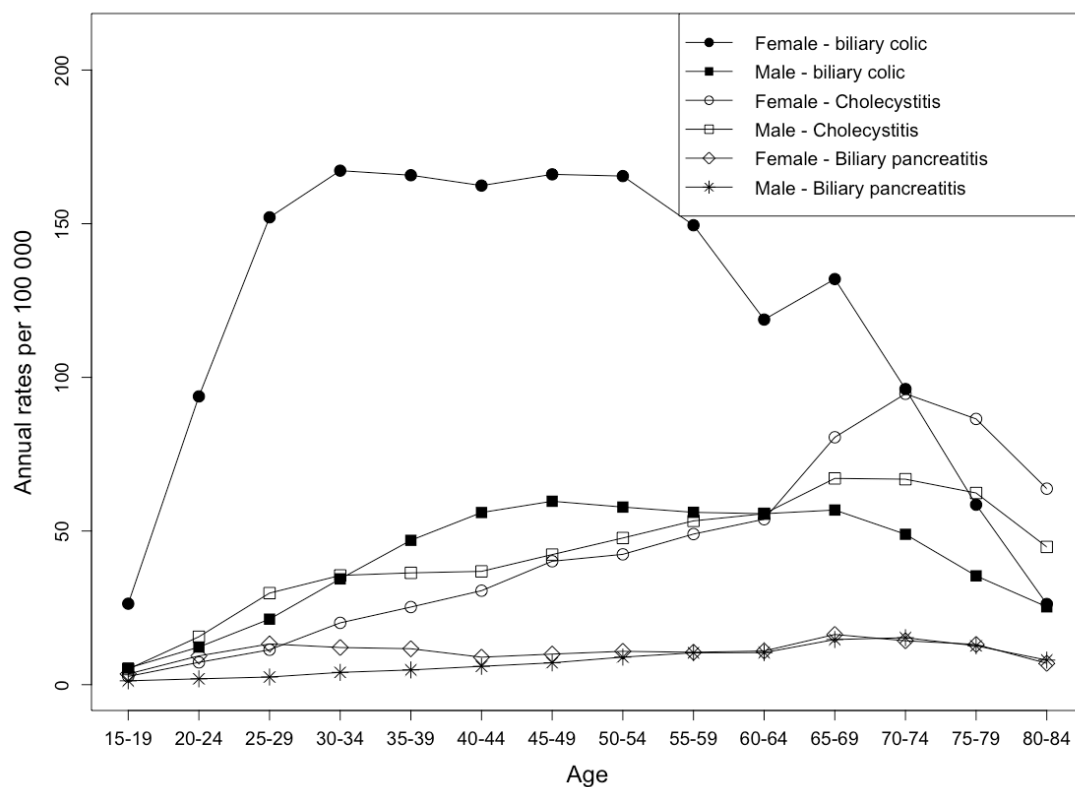
In addition, another known disadvantage of the rendezvous intraoperative ERCP is the prolonged operation time. We reported a median operation time of 186 minutes including ERCP time of at least 30 minutes. The proportion of the successful rendezvous cannulations and the total operation time remained relatively stable during the study period. This was probably due to the complexity of the patients and the continuous turnover of surgeons and endoscopists involved.

Other reported disadvantages of the rendezvous technique are organizational and logistical. These obstacles were managed by integrating the ERCP-equipment and personnel in the surgical team. This study, being of a retrospective design and representing a single-center experience, is subject to selection bias and limited external validity. On the other hand, a major strength of the study is the large number of patients treated by the intraoperative rendezvous ERCP during cholecystectomy.

## 4.2 PAPER II:

### 4.2.1 Cholecystectomies in Sweden:

A total of 178 441 cholecystectomies were registered in the IPR between 1998 and 2013. The annual age and gender-adjusted rates per 100 000 inhabitants were calculated for the 21 Swedish counties. There was a two-fold variation in the cumulative annual cholecystectomy rates among the Swedish counties (ranging from 100 in Örebro to 207 in Jämtland, per 100000 inhabitants). Most cholecystectomies were performed on young females with uncomplicated biliary colic. Cholecystectomies for GSC were mainly performed in older age groups with no obvious differences between both genders. **Figure 6**, demonstrates the distribution of cholecystectomy indications from GallRiks.



**Figure 6.** The distribution of cholecystectomy indications related to age and gender from GallRiks.

### 4.2.2 Gallstone complications (GSC):

K85 – pancreatitis and K81 – cholecystitis rates were also extracted from the IPR for the same period between 1998 and 2013. The age and gender-adjusted rates were calculated per 100 000 inhabitants and year. Annual rates for the Swedish counties were similarly calculated for gallstone pancreatitis and cholecystitis obtained from the GallRiks between 2006 and

2013. The remaining indication for cholecystectomy (uncomplicated biliary colic) was analyzed in a similar fashion and annual rates obtained from GallRiks between 2006 and 2013. **Table 3**, shows the variations in the adjusted annual rates of the extracted variables.

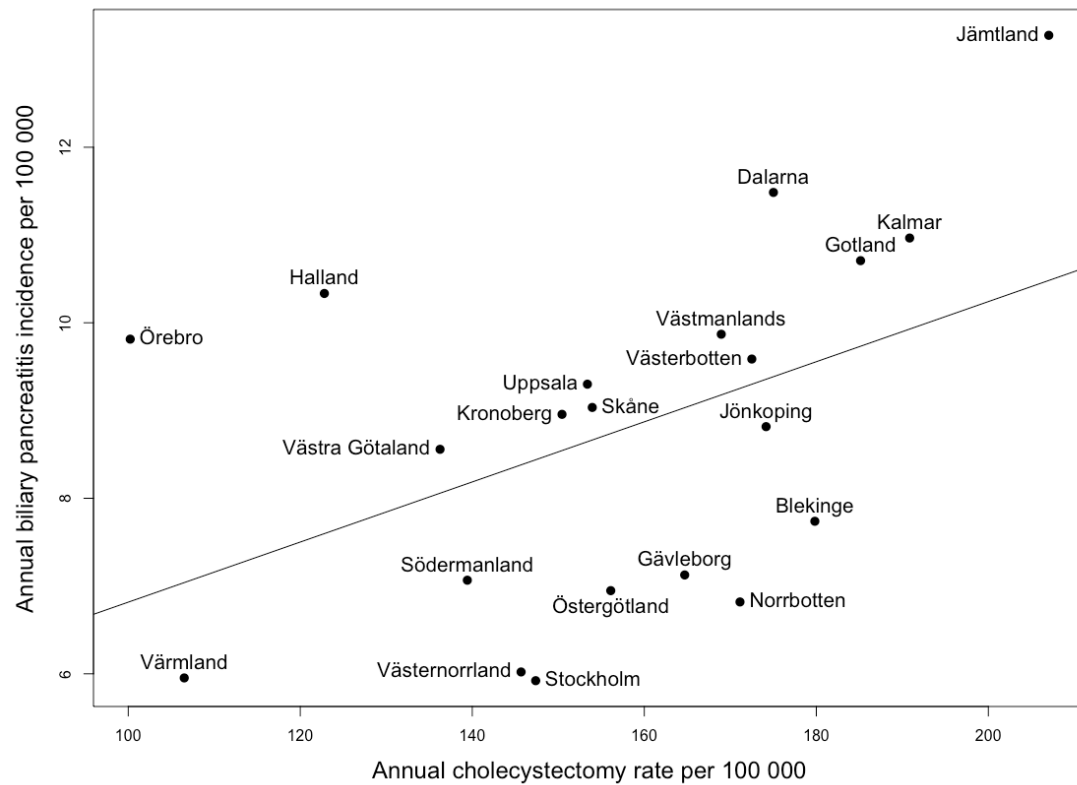
**Table 3.** *Adjusted annual rates of cholecystectomy and admission rates for K85-pancreatitis, K81-cholecystitis from the IPR and of biliary pancreatitis, cholecystitis and biliary colic from GallRiks among the Swedish counties.*

Variable	Range	Mean	Median	95 % CI
<b>Cholecystectomy</b>	100 – 207	157	156	145 – 169
<b>K85- Pancreatitis</b>	34 – 50	42	41	40 – 44
<b>K81- Cholecystitis</b>	17 – 32	24	26	22 – 26
<b>Biliary pancreatitis</b>	6 – 13	9	9	8 – 10
<b>Cholecystitis</b>	24 – 54	38	39	35 – 42
<b>Biliary colic</b>	60 – 117	85	84	78 – 92

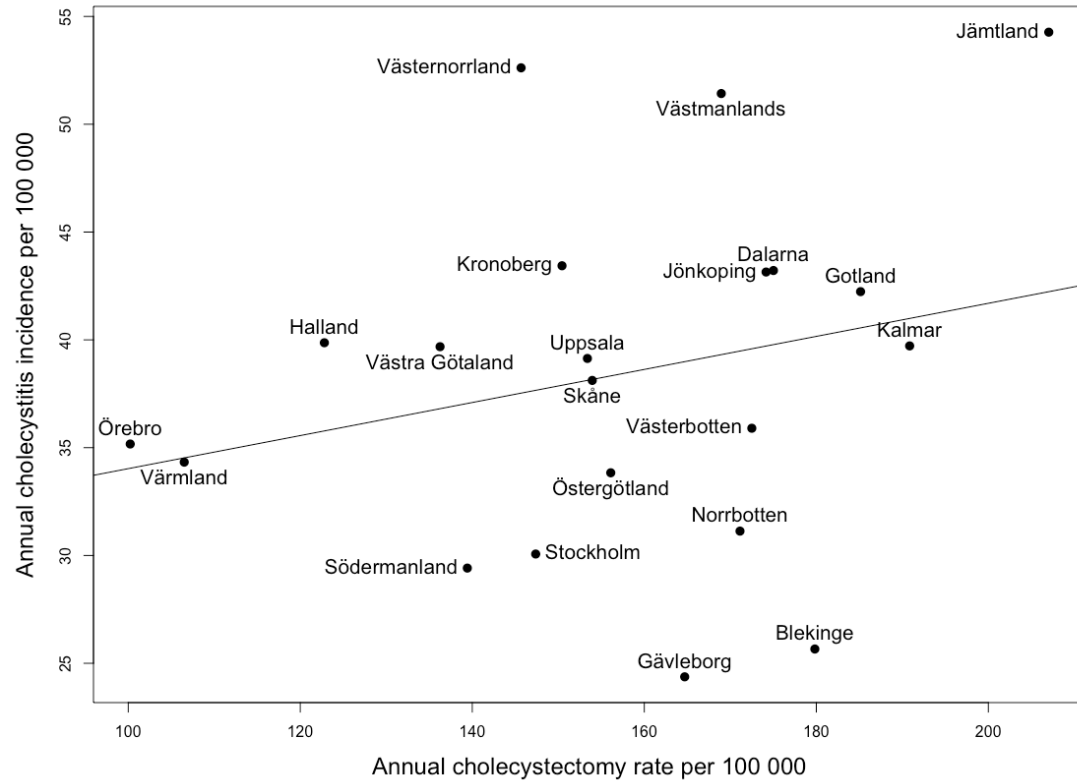
#### 4.2.3 Impact of cholecystectomy rate on GSC:

The annual cholecystectomy rates were plotted against the annual gallstone pancreatitis (**Figure 7**) and cholecystitis (**Figure 8**) incidences from GallRiks. The correlations were analyzed by linear regression model. We found no inverse correlation between the cholecystectomy rates and GSC as hypothesized. Instead, the correlations demonstrated a slightly positive correlation for gallstone pancreatitis (adjusted  $R^2$  0.167,  $p = 0.037$ ) and cholecystitis (adjusted  $R^2$  0.013,  $p = 0.273$ ).





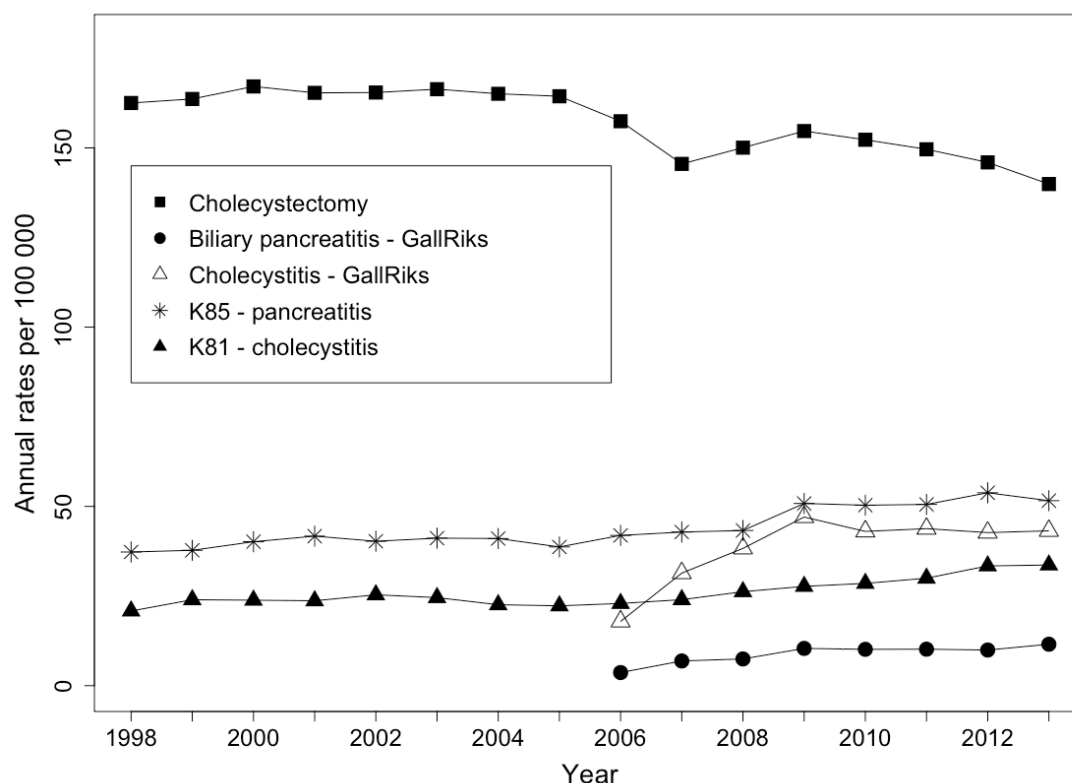
**Figure 7.** Scatterplot of annual rates of cholecystectomy and biliary pancreatitis. Adjusted  $R^2$  0.167,  $p=0.037$ .



**Figure 8.** Scatterplot of annual rates of cholecystectomy and cholecystitis. Adjusted  $R^2$  0.013,  $p=0.273$ .

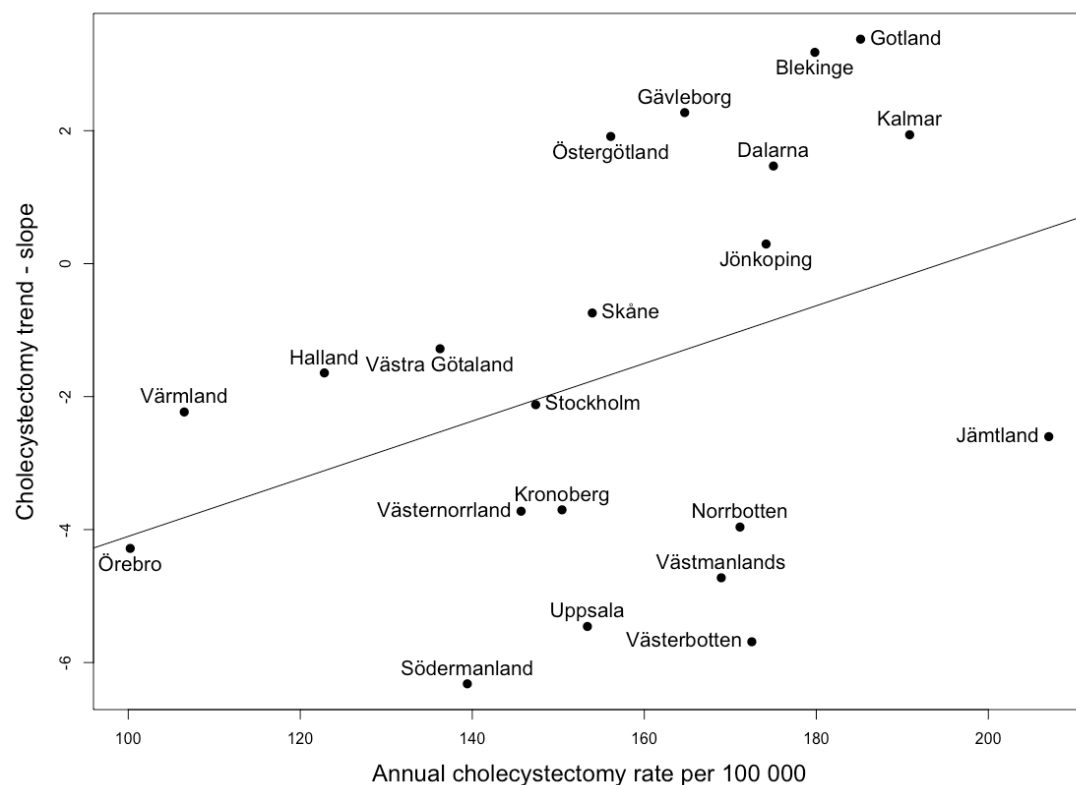
#### 4.2.4 Cholecystectomy trends in Sweden:

The annual rate of cholecystectomies remained stable between 1998 and 2013 (**Figure 9**). The counties continued to perform cholecystectomies at rates irrespective if they were high- or low-operating units.



**Figure 9.** Trends of total number of cholecystectomies, K81 cholecystitis and K85 pancreatitis from the IPR, and biliary pancreatitis and cholecystitis from GallRiks.

The change in the operating rate over time was plotted against the annual cholecystectomy rates for the Swedish counties. The resulting scatterplot is shown in **Figure 10**. The correlation was tested by linear regression and turned out to be weak and statistically not significant (adjusted  $R^2$  0.096,  $p=0.092$ ). The changing cholecystectomy rates for each Swedish county was used to predict eventual impact on the GSC – biliary pancreatitis and cholecystitis. The correlations were weak and not statistically significant (adjusted  $R^2$  were – 0.039 and –0.011, and  $p=0.635$  and 0.393 respectively) indicating that the changing annual cholecystectomy rates did not affect the GSC rates.



**Figure 10.** Scatterplot of cholecystectomy rates and cholecystectomy trends. Adjusted  $R^2$  0.096,  $p=0.092$ .

#### 4.2.5 Comments:

This study revealed a wide variation in the annual cholecystectomy rates between the 21 Swedish counties during the study period. There was a two-fold difference between Örebro and Jämtland counties (100 vs. 207 cholecystectomies per year and 100 000 inhabitants) with most these cholecystectomies were performed laparoscopically. With the advent of minimally invasive surgery, rates of procedures such as laparoscopic cholecystectomy has increased globally [Urbach and Stukel 2005]. Cholecystectomy rates are known to vary between countries and perhaps also within countries [Halldestam et al. 2004].

These demonstrated variations in cholecystectomy rates can barely be explained by differences in gallstone prevalence in Sweden. In this context, it is important to highlight that most cholecystectomies in our study were performed on younger females with uncomplicated biliary colic as indication. Another finding in this study was the changing annual cholecystectomy rates for the Swedish counties over time. Cholecystectomy rates decreased in most counties during the study period and this contributed to a slight decrease in the overall annual rate in Sweden between 1998 and 2013.

The annual rates of gallstone complications, pancreatitis and cholecystitis, for the different Swedish were similarly calculated. When these rates were correlated together by linear regression models, none showed inverse correlation indicating a protective effect of the high cholecystectomy rates.

The strength of the study lies in its nationwide coverage with almost a 15-year period. This is important when studying the long-term effects of gallstones such as gallstone pancreatitis and cholecystitis. At the same time, covering a large number of cholecystectomies is essential to increase the power to detect differences. There is a need to rely on population-based studies when randomized studies would require large number of patients and longtime of follow-up.

Selection bias might have occurred, for example, elderly patients with complicated gallstone disease who were unfit for surgery are not included in the data retrieval from GallRiks.

This study has highlighted important aspects of gallstone surgery in Sweden. It has demonstrated differences not only in cholecystectomy rates, but also in the changing rates over time. This indicates that cholecystectomy is a surgical procedure that is still subject to local surgical culture.

### 4.3 PAPER III:

#### 4.3.1 The RV populations – baseline characteristics:

The search results from GallRiks yielded 5333 ERCP procedures. The procedures performed by the RV technique were included in the study and divided into RVIO ERCP (n=1205) and RVPO ERCP (n=565). Hence, the RV technique was used in about 33% of the total number of ERCP procedures performed during the study period. The two groups were similar in baseline characteristics, **Table 4**.

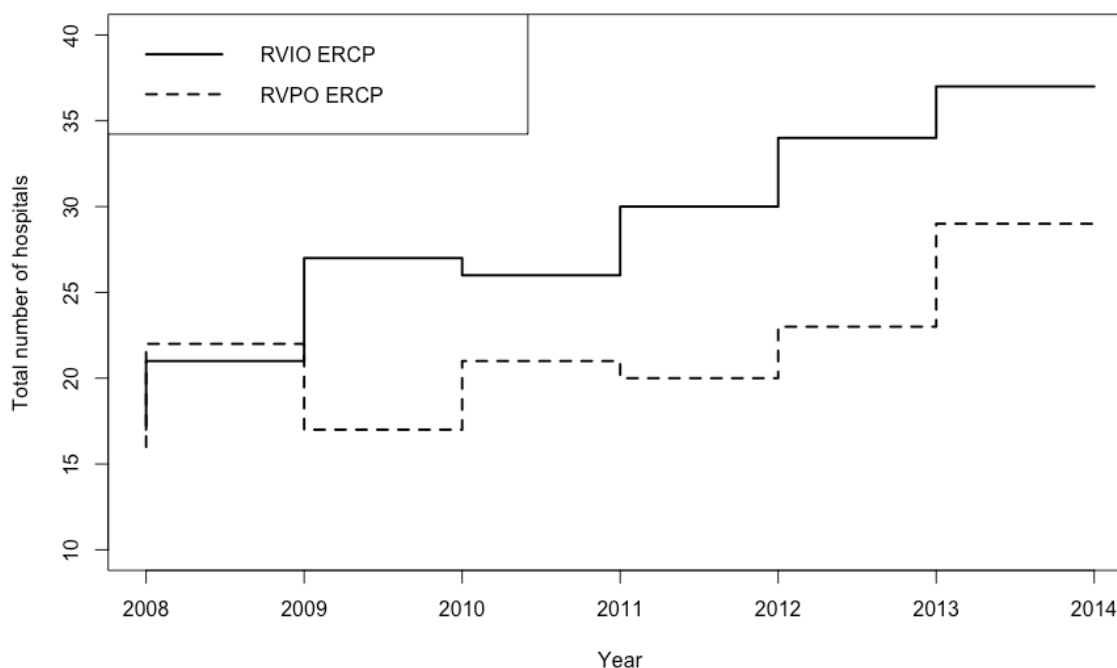
*Table 4. Baseline characteristics of the study populations.*

	RVIO	RVPO	<i>p</i> -value
<b><i>Patient characteristics</i></b>			
Total number of RV ERCP procedures	1205	565	
Age (mean)	52 (17.8) *	52 (17.1) *	0.64
Female: male ratio	1.98	1.92	
Total number of clinics utilizing rendezvous technique	46	41	
<b><i>ERCP characteristics</i></b>			
ERCP procedure time in minutes†	30 (6-347)	25 (8-179)	<b>&lt;0.001</b>
No previous sphincterotomy (%)	1173 (97)	544 (96)	0.086
Beside-the-guidewire technique (%)	211 (17.5)	193 (34)	<b>&lt;0.001</b>
<b><i>Cholecystectomy characteristics</i></b>			
Operation time in minutes (min) †	140 (35-565) ‡	128 (35-600)	<b>&lt;0.001</b>
Time from cholecystectomy to ERCP (days)†	0 (0)	1 (0-30)	<b>&lt;0.001</b>
Time from ERCP to discharge (days)†	2 (0-189)	3 (0-182)	<b>&lt;0.001</b>

\*Standard deviation. † Median. ‡ including ERCP time. Bold style indicates statistical significance. RVIO: rendezvous intraoperative. RVPO: rendezvous postoperative.

### 4.3.2 The rendezvous technique in Sweden:

The total number of Swedish hospitals utilizing both RV techniques has increased between 2008 and 2014, **Figure 11**.



**Figure 11.** The trend of rendezvous technique in Sweden. RVIO: rendezvous intraoperative. RVPO: rendezvous postoperative. ERCP: endoscopic retrograde cholangiopancreatography.

### 4.3.3 Post-ERCP pancreatitis:

The overall PEP rate was 4.3%. Higher PEP rate was observed in RVPO group compared with RVIO group in the univariate analysis (6.4% vs. 3.2%,  $p=0.003$ ). To assess the impact of the cannulation technique on the PEP rate, a subgroup analysis was run, including only patients with over-the-guidewire technique. The model was unaffected and the RVPO technique (OR 2.67, 95% CI 1.48 – 4.90,  $p=0.001$ ) and pancreatic duct cannulation (OR 2.60, 95% CI 1.14 – 5.40,  $p=0.015$ ) were independently associated with increased PEP rate. The final multivariate PEP model is presented without the cannulation technique variable (**Table 5**). Similarly, the hospital caseload and endoscopist load showed no effect on the outcome and thus were removed.

**Table 5.** The multivariate model detecting Post-ERCP pancreatitis.

	Post-ERCP pancreatitis		
	Odds Ratio	CI	p-value
(Intercept)	0.03	0.01 – 0.08	<0.001
Unintentional pancreatic duct cannulation	2.60	1.14 – 5.40	<b>0.015</b>
RVPO technique	2.67	1.48 – 4.90	<b>0.001</b>
Gender – female	1.32	0.76 – 2.40	0.337
ERCP procedure time (min)	1.01	1.00 – 1.02	<b>&lt;0.001</b>
Age (years)	0.98	0.97 – 1.00	<b>0.011</b>
Time between ERCP and discharge (days)	1.06	1.03 – 1.09	<b>&lt;0.001</b>
Time between cholecystectomy and ERCP (days)	0.91	0.75 – 1.02	0.222
Observations	1662		

Bold style indicates statistical significance. RVPO: rendezvous postoperative. CI: confidence interval.

#### 4.3.4 Postoperative infections:

The rate of postoperative infections was higher in the RVPO group compared with the RVIO group (4.4% vs. 2.3%,  $p=0.028$ ). In the multivariate analysis adjusted for age, gender and the other factors showed in **Table 6**, the RVPO was associated with higher risk for postoperative infections (OR 2.13, 95% CI 1.05 – 4.33,  $p=0.036$ ). Both postoperative bleeding and bile leakage increased the risk for postoperative infections dramatically. The risk for postoperative infections was lower when antibiotics were used, however the correlation was not statistically significant in the case of antibiotic therapy.

#### 4.3.5 Hospital stay:

Patient who received RVIO ERCP had a combined cholecystectomy and ERCP during the same anaesthetic session. On the contrary, patients who had cholecystectomy and a subsequent RVPO ERCP, had to wait one day (median) for the ERCP. Further, patients who received RVPO ERCP stayed one additional day after the ERCP procedure compared with the RVIO (median 3 days vs. 2 days,  $p<0.001$ ).

**Table 6.** Postoperative infection multivariate model.

	Postoperative infections		
	<i>Odds Ratio</i>	<i>CI</i>	<i>p-value</i>
(Intercept)	0.00	0.00 – 0.02	<0.001
Antibiotic usage			
- Prophylaxis	0.37	0.16 – 0.77	<b>0.010</b>
- Therapy	0.51	0.21 – 1.13	0.108
Age (years)	1.03	1.01 – 1.05	<b>0.008</b>
Gender – female	0.69	0.37 – 1.30	0.246
RVPO ERCP technique	2.13	1.05 – 4.33	<b>0.036</b>
Time between cholecystectomy and ERCP (days)	0.97	0.83 – 1.07	0.593
Time between ERCP and discharge (days)	1.04	1.02 – 1.07	<b>0.003</b>
Cholecystectomy duration (min)	1.00	1.00 – 1.01	0.096
Bile leakage	5.62	1.74 – 15.57	<b>0.002</b>
Bleeding	13.81	4.86 – 36.23	<b>&lt;0.001</b>
Observations		1658	

Bold style indicates statistical significance. RVPO: rendezvous postoperative.



#### 4.3.6 Other complications:

Overall morbidity was higher in the RVPO ERCP group compared with the RVIO group (20% vs. 14%,  $p=0.004$ ), **Table 7**.

*Table 7. Complications to the rendezvous ERCP and cholecystectomy.*

	RVIO (%)	RVPO (%)	<i>p</i> -value
<b>Completed 30 days' follow-up</b>	1121 (93)	544 (96)	
<b>Overall complications</b>	157 (14)	107 (19.7)	<b>0.004</b>
<b>Post-ERCP pancreatitis</b>	36 (3.2)	35 (6.4)	<b>0.003</b>
<b>Perforation</b>	3 (0.3)	2 (0.4)	0.66*
<b>Bleeding</b>	21 (1.9)	7 (1.3)	0.43*
<b>Infections including deep abscesses</b>	26 (2.3)	24 (4.4)	<b>0.028</b>
<b>Bile leakage</b>	18 (1.6)	14 (2.6)	0.24
<b>Cholangitis</b>	11 (1)	7 (1.3)	0.62*
<b>Retained common bile duct stones</b>	7 (0.6)	30 (5.5)	<b>&lt;0.001</b>
<b>Thromboembolism</b>	5 (0.5)	2 (0.4)	1.00*

\*Fisher's exact test. Bold style indicates statistical significance. RVIO: rendezvous intraoperative. RVPO: rendezvous postoperative.

#### 4.3.7 Stone clearance:

There was no difference in the reported stone clearance rates between the RVPO and RVIO groups. However, there was a higher rate of retained stones in the RVPO compared with the RVIO group (5.5% vs. 0.6%,  $p<0.001$ ). In addition, there was a higher rate of negative cholangiographic findings in the RVPO group (20.5% vs. 11%,  $p<0.001$ ). **Table 8**, demonstrates the different stone clearance rates in different stone categories.

*Table 8. Stone clearance rates in different stone categories.*

	RVIO (%)	RVPO (%)	<i>p</i> -value
<b>Reported clearances</b>	1118 (93)	531 (94)	
<b>Overall complete stone clearance</b>	865 (77.3)	380 (71.5)	0.37
<b>1 stone</b>	359 (32.1)	160 (30.1)	0.59
<b>2-5 stones</b>	409 (36.6)	192 (36.1)	0.95
<b>6-10 stones</b>	65 (5.8)	21 (3.9)	0.16
<b>&gt; 10 stones</b>	32 (2.9)	7 (1.3)	0.07
<b>Uncertain finding</b>	30 (2.7)	14 (2.6)	1.00
<b>No stones found</b>	124 (11)	109 (20.5)	<b>&lt;0.001</b>

Bold style indicates statistical significance. RVIO: rendezvous intraoperative. RVPO: rendezvous postoperative.

#### 4.3.8 Cannulation technique:

Cannulation by beside-the-guidewire technique was used more frequently in the RVPO ERCP technique compared with the RVIO ERCP, see **Table 4** ( $p<0.001$ ).

#### 4.3.9 Comments:

To study the evolution and impact of the rendezvous ERCP on postoperative morbidity in Sweden, a nationwide registry study was conducted. In the last decades, the rendezvous technique has been implemented in several Swedish units/hospitals. In addition, the rendezvous technique has been subjected to modifications such as the rendezvous postoperative ERCP. These two approaches dominating the rendezvous techniques in Sweden were hitherto unstudied in terms of morbidity.

The main finding of the study was the higher overall complication rate in the rendezvous postoperative technique compared with the rendezvous intraoperative technique (20% vs. 14%,  $p=0.004$ ). This was mainly represented by the higher rates of PEP (6.4% vs. 3.2%,  $p=0.003$ ) and postoperative infections (4.4% vs. 2.3%,  $p=0.028$ ).

To further study these variables in our population, multivariate logistic regression was used and several potential confounding factors were considered. Factors such as pancreatic duct cannulation, gender, age, ERCP time, and the type of rendezvous technique were used to adjust for the risk of PEP. For unknown reasons, the situation was further complicated when the rendezvous cannulation technique was further modified into either using the existing guidewire served by the surgeon to cannulate (over-the-wire technique) or by using another guidewire beside the existing one (beside-the-wire technique). This specific detail is of crucial importance, as the “beside-the-wire” technique might have potentially resulted in unintentional pancreatic duct cannulation and theoretically increase the risk of PEP. The beside-the-wire technique was practiced more frequently in the rendezvous postoperative technique group of patients. In addition, hospital and endoscopist volumes, factors that can potentially affect the risk of PEP, were also used in the multivariate logistic model.

The result showed that unintentional pancreatic duct cannulation and the rendezvous postoperative technique were independently associated with increased risk of PEP. In line with previous studies, factors such as ERCP time, female gender (although not statistically significant) and hospital stay after the ERCP were also associated with increased risk of PEP [Freeman 2012; Swahn et al. 2013a]. The time between the cholecystectomy and the ERCP was not associated with increased risk of PEP. In addition, hospital and endoscopist ERCP volumes did not show any impact to increase the risk of PEP.

Postoperative bleeding, bile leak, the rendezvous postoperative technique, hospital stay after the ERCP, and age were factors associated with increased risk of postoperative infections. The time spend between the cholecystectomy and the ERCP together with cholecystectomy time did not affect the risk of postoperative infections. On the other hand, antibiotic usage and antibiotic prophylaxis reduced the risk of postoperative infections. The association between the increased PEP and postoperative infection rates and hospital stay after the ERCP does not necessarily mean a causality, as a reverse causality can explain the association and is probably more likely.

Despite the study showed similar stone clearance rates in both rendezvous techniques, there was higher rate of negative ERCP procedures in the rendezvous postoperative technique (20.5% vs. 11%,  $p<0.001$ ). Stones may be pushed by the guidewire or pass spontaneously while the patient is waiting for the ERCP procedure the next day. In addition, another important finding was the increased rate for retained stones in the rendezvous postoperative technique (5.5% vs. 0.6%,  $p<0.001$ ).

The study has its strength in the large number of ERCP procedures performed by the rendezvous technique and its national coverage. Indeed, it is the first study that reports the impact of the rendezvous postoperative ERCP technique on morbidity.

## 4.4 PAPER IV:

### 4.4.1 The study population:

A total of 472 patients were admitted with acute pancreatitis between May 2009 and July 2017. Of these, 154 patients with gallstone pancreatitis were eligible, 88 patients denied participation. Sixty-six patients were enrolled and assigned to either index cholecystectomy (IC, n=32) or scheduled cholecystectomy (SC, n=34). The baseline characteristics are shown in **Table 9**.

*Table 9. Baseline characteristics of the randomized patients.*

Parameter	IC (n=32)	SC (n=34)	p-value
Age (years)	48 (24-75)	43.5 (20-78)	0.32
Gender (female: male)	20:12	19:15	0.76
CRP at admission	13.5 (1 - 238)	10.5 (1-313)	0.74
BMI	28 (22 - 42)	27 (17 - 43)	0.37
ASA class (I: II: III)	18:12:2	18:14:2	0.95
Days between admission to randomization	2 (0-4)	1 (0-4)	0.07
Total hospital stay at admission (days)	5 (2-8)	3 (1-14)	<b>0.02</b>

Data presented as median and range. CRP: C-reactive protein (mg/L). BMI: Body Mass Index (kg/m<sup>2</sup>). ASA: American Society of Anesthesiologists. IC and SC: index and scheduled cholecystectomy. Bold style indicates statistical significance.

### 4.4.2 Gallstone-related complications:

Overall gallstone-related complications occurred in nine patients in the SC group consisting of five patients with recurrent gallstone pancreatitis and four patients with recurrent biliary

colic requiring early cholecystectomy (26.4% vs. 3.1%,  $p=0.013$  – Fisher’s exact test). One patient in the IC group did not undergo early cholecystectomy due to shortage of operation resources at the same-admission. This patient recurred in severe recurrent pancreatitis. There were no admissions due to recurrent cholangitis or cholecystitis.

#### 4.4.3 Cholecystectomy-related complications:

Complications to cholecystectomy occurred in two patients in the SC group compared with one patient in the IC group. These consisted of pancreatitis and sub-phrenic abscess in the SC group and surgical site infection in the IC group (7.1% vs. 3.2%,  $p=0.6$ ). The duration of the cholecystectomy was significantly longer in the IC group (median 120 min vs. 89 min,  $p<0.01$ ). **Table 10** summarized results related to the cholecystectomies.

**Table 10.** *The characteristics of the received cholecystectomies.*

Parameter	IC (n=31)	SC (n=28)	<i>p</i> -value
Hospital stay after cholecystectomy (days) *	1 (1-3)	1 (0-4)	<b>0.01</b>
Days from randomization to cholecystectomy *	1 (0-4)	50 (1-434)	<b>&lt;0.01</b>
Cholecystectomy time (minutes) *	120 (45-210) ‡	89 (36-145) ‡	<b>&lt;0.01†</b>
Operative technique (laparoscopic: open: converted) *	28:1:2	28:0:0	0.49
Operative finding (acute cholecystitis: chronic cholecystitis: normal gallbladder)	(5:1:25)	(0:4:24)	<b>0.046</b>

\* Per protocol analysis. † t-test performed. ‡ ERCP time removed. Bold style indicates statistical significance. IC and SC: index and scheduled cholecystectomy.

#### 4.4.4 Common bile duct stones and ERCP:

Common bile duct stones were detected by the intraoperative cholangiogram in three patients in the SC compared with seven patients in the IC group (10.7% vs. 22.5%,  $p=0.3$ ). These were successfully treated by intraoperative ERCP.

#### 4.4.5 Patients' reported outcomes – SF-36 and pain:

The SF-36 questionnaires were returned by 27/32 and 27/34 patients in the IC and SC groups, respectively. The transformed scores of the SF-36 questionnaire did not differ between the two groups at randomization (**Table 12**). Among these scores, pain and emotional well-being improved (statistically significant) between IC and SC groups at follow-up and for IC between randomization and follow-up. Pain reported by the VAS show significant reduction in the IC group at follow-up (**Table 11**).

***Table 11.** The reported pain by the visual analogue scale (VAS) at randomization and follow-up for Index cholecystectomy and scheduled cholecystectomy.*

Outcome	IC (n=27)	SC (n=27)	<i>p</i> -value
<b>Pain at randomization</b>	2 (0-6.8)	1.5 (0-7)	0.33
<b>Pain at follow-up</b>	0 (0-5)	0 (0-3.2)	0.64
<b><i>p</i>-value</b>	<b>&lt;0.01</b>	0.08	

Bold style indicates statistical significance. IC and SC: index and scheduled cholecystectomy.

**Table 12.** The transformed scores from the reported SF36 by patients randomized to Index Cholecystectomy (IC) and Scheduled Cholecystectomy (SC) at randomization and Follow-up.

	Randomization		Follow-up		p-Values			
	IC	SC	IC	SC	P1	P2	P3	P4
	Median (range)	Median (range)	Median (range)	Median (range)				
<b>Physical functioning</b>	85 (0 – 100)	75 (0 – 100)	95 (25 – 100)	95 (10 – 100)	0.15	0.52	0.10	<b>&lt;0.01</b>
<b>Role limitations due to physical health</b>	100 (0 – 100)	100 (0 – 100)	100 (0 – 100)	100 (0 – 100)	0.84	0.72	0.87	0.70
<b>Role limitations due to emotional problems</b>	100 (0 – 100)	100 (0 – 100)	100 (0 – 100)	100 (0 – 100)	0.79	0.16	0.14	0.70
<b>Energy/fatigue</b>	65 (0 – 100)	65 (0 – 90)	60 (5 – 100)	60 (0 – 100)	0.13	0.17	0.73	0.94
<b>Emotional well-being</b>	80 (28 – 100)	76 (28 – 96)	88 (20 – 100)	84 (40 – 100)	0.42	<b>0.04</b>	<b>0.04</b>	0.22
<b>Social functioning</b>	81.25 (12.5 – 100)	87.5 (25 – 100)	100 (12.5 – 100)	100 (37.5 – 112.5)	0.56	0.65	0.07	0.43
<b>Pain</b>	57.5 (0 – 100)	55 (0 – 100)	83.75 (32.5 – 100)	77.5 (10 – 100)	0.73	<b>&lt;0.01</b>	<b>&lt;0.01</b>	0.08
<b>General health</b>	75 (0 – 100)	79 (25 – 95)	75 (0 – 100)	75 (45 – 100)	0.07	0.10	0.77	0.58

P1 and P2 are p-values for differences between IC and SC at randomization and follow-up. P3 and P4 are p-values for differences between randomization and follow-up for IC and SC respectively. Bold style indicates statistical significance.

#### 4.4.6 Comments:

The main finding in this study is represented by the increased risk for gallstone-related complications if cholecystectomy was delayed from the initial episode of acute gallstone pancreatitis compared to if cholecystectomy was performed during the same admission (26.4% vs. 3.1%,  $p=0.013$ ). The results are comparable with previously reported risk of recurrent pancreatitis, although our study reports somewhat higher pancreatitis rate (14.7%) compared to the multicenter PONCHO trial (9%) [da Costa et al. 2015].



Our study is the first study to report patients' well-being and pain. The results of SF36 questionnaire demonstrated that several scores including role limitation due to physical health, general health, energy/fatigue, and social functioning did not show any significant change at follow-up. Only pain and emotional well-being improved at follow-up. It is normal that pain is the predominant symptom in patients with mild gallstone pancreatitis. Although the majority recover quickly, a high proportion (up to 50%) still experience biliary colic while waiting for cholecystectomy.

## **5 DISCUSSION**

### **5.1 GENERAL DISCUSSION:**

#### **5.1.1 The rendezvous technique:**

The term “rendezvous” has been used in literature to describe techniques when the use of the guidewire was totally omitted or used only selectively. Sometimes the term “rendezvous” has been used to describe only the combined laparoendoscopic procedure to treat concomitant common bile duct regardless if a guidewire was used [Basso et al. 1999; Cemachovic et al. 2000; Kalimi et al. 2000; Tatulli and Cuttitta 2000; Iodice et al. 2001; Meyer et al. 2002; Williams and Vellacott 2002; Wright et al. 2002; Wei et al. 2003; Hong et al. 2006; La Greca et al. 2007; ElGeidie et al. 2011].

In this context, it is crucial to emphasize the importance of a guidewire to facilitate cannulation of the bile ducts and consequently avoiding multiple cannulation attempts and unintentional pancreatic duct cannulation. We believe that intraoperative ERCP with rendezvous technique that utilizes the full advantage of the an antegrade guidewire should be considered as the only genuine method. It is therefore, of high importance to have a conceptual consensus regarding the terminology of the “rendezvous” technique. Throughout this thesis, the term “rendezvous” is used only to refer to guidewire-assisted cannulation.

### **5.2 WHAT IS THE RISK FOR POST-ERCP PANCREATITIS IN RENDEZVOUS INTRAOPERATIVE ERCP?**

It is still a common practice worldwide to manage common bile duct stones by preoperative ERCP prior to cholecystectomy. ERCP in general is associated with two main risks; cannulation failure and PEP. Accidental pancreatic duct cannulation during ERCP is one of the identified risk factors to develop PEP.

The rendezvous IOERC has been in clinical practice at the Karolinska University Hospital since the late 1990s. To evaluate the complication rate and stone clearance rate of the technique, a retrospective study was conducted. The study demonstrated a significantly lower risk for PEP in the patients who had a rendezvous cannulation compared with patients who had a conventional ERCP performed intraoperatively. The low PEP rate is in line with previously reported rates by several case-series on RV ERCP [Iodice et al. 2001; Tricarico et al. 2002; Saccomani et al. 2005; Lella et al. 2006; Ghazal et al. 2009; Tzovaras et al. 2010]. However, based on the results from study III in this thesis, a higher PEP rate (3.2% for the RVIO and 4.3% for both techniques) was demonstrated after RVIO ERCP. This can be explained by the diversity of hospitals and endoscopists involved and their contributing learning curves.

### **5.3 CAN HIGH CHOLECYSTECTOMY RATE PREVENT GALLSTONE COMPLICATIONS?**

To investigate the impact of cholecystectomy on the gallstone complications, a nationwide registry-based study was conducted. The hypothesis was that a high cholecystectomy rate would have a preventive effect on gallstone complications – acute cholecystitis and acute pancreatitis. The annual rates for cholecystectomy and gallstone complications were obtained from the national inpatient registry (IPR) and the national registry for gallstone disease and ERCP (GallRiks). The annual cholecystectomy rates varied two-fold between the Swedish counties. The cholecystectomy and the corresponding gallstone complication rates were correlated in linear regression models. The results demonstrated that the variation in the gallstone complication rates could not be completely explained by the variation in cholecystectomy rates. Second, the correlation was not inversely oriented indicating a protective effect of cholecystectomy.

### **5.4 IS RENDEZVOUS INTRAOPERATIVE ERCP TECHNIQUE APPLICABLE IN A SMALL-VOLUME COUNTY HOSPITAL?**

The results from paper III demonstrated clearly a positive trend represented by the increasing number of Swedish hospitals adopting the RV technique between 2008 and 2014. To achieve a functioning rendezvous intraoperative ERCP, a number of practical and/or technical aspects are required. The most important factor is to handle the logistical, collaborative and organizational difficulties if ERCP is not an integrated part of the surgical team. These are normally caused by the inability of arranging ERCP in the operating room and coordinating operation and endoscopy lists [Tricarico et al. 2002; Saccomani et al. 2005; Lella et al. 2006; La Greca et al. 2007]. There is also a need for a well-functioning communication between the involved departments and a predefined algorithm about the workflow especially regarding setup of the equipment. We know through personal experience and communication that training operation nurses in some centers to assist at the ERCP procedure has been one breakthrough to solve organizational issues with the RV technique.

The use of IOC is a prerequisite for the RV ERCP. The ideal method and the timing to diagnose CBDS is still debated. While some authors advocate non-invasive methods like preoperative MRCP or ultrasound [Spinn et al. 2010], others do not use IOC routinely [Altieri et al. 2017]. In the context of the RV ERCP, the immediate detection of CBDS is mandatory in order to avoid unnecessary ERCP, as CBDS can migrate and pass spontaneously [Acosta et al. 1977].

Another fundamental aspect is that the rendezvous cannulation is completely dependent on a successful guidewire placement passing through the ampulla. It is therefore, important to make efforts to pass the guidewire. Using the cholangiography forceps instead of a loosely applied clip on the cholangiography catheter allows for a better handling of the guidewire.

Can the “novice” or unexperienced endoscopist perform a RV ERCP? Technical difficulties can arise from the supine positioning of patient or from gas distension of the bowel from endoscopy [Meyer et al. 2002; Elgeidie et al. 2017; Tan et al. 2017]. While some authors advocated the availability of skilled endoscopists or specialists experience in both laparoscopy and ERCP [Wang et al. 2013; El Nakeeb et al. 2015], others completed the LC and repositioned the patient to left lateral [Elgeidie et al. 2017]. From paper I, we know that tens of surgical trainees and endoscopy fellows were involved in the care of patients. In addition, low hospital- and endoscopist ERCP volume could not be demonstrated to increase the risk of PEP in paper III.

Finally, it is important to create teaching platforms like endoscopy fellowships to train endoscopist and to increase the awareness by surgeons and endoscopists to the importance of the RV technique. **Figure 12** is a flowchart demonstrating some practical aspects of the rendezvous intraoperative ERCP.

## **5.5 IS RENDEZVOUS ERCP PERFORMED DURING CHOLECYSTECTOMY SUPERIOR TO RENDEZVOUS ERCP PERFORMED POSTOPERATIVELY?**

Huntington and Bohlman were the first who reported in 1997 the modified postoperative RV technique in 14 patients [Huntington and Bohlman 1997]. The technique was successful in only 9 patients, where the guidewire could be retrieved. The main problem was guidewire migration. Generally, the adverse effects associated with the rendezvous postoperative ERCP were not studied in larger populations. In Sweden, the rendezvous postoperative technique was introduced by several hospitals as an alternative to the rendezvous intraoperative technique. To study the technique, the rendezvous postoperative ERCP were compared to the rendezvous intraoperative technique. Data on the rendezvous ERCP procedures were obtained from the GallRiks between 2008 and 2014.

The results in this study clearly demonstrated the superiority of the RV intraoperative technique, in terms of reduced PEP and postoperative infection rates. In addition, there was higher negative cholangiographic findings (negative ERCP) probably explained by the stone passage to the duodenum either spontaneously or being pushed by the guidewire. The higher rate of retained common bile duct stones in the RV postoperative technique can be explained by the suboptimal clearance of the cystic duct postoperatively caused by the caution not to dislodge the laparoscopically applied cystic clips.

## **5.6 WHEN TO PERFORM CHOLECYSTECTOMY IN MILD GALLSTONE PANCREATITIS?**

This topic is still debated, although previous randomized controlled trials have demonstrated a clear increase in the risk for recurrent biliary events in patients with mild gallstone pancreatitis while waiting for elective cholecystectomy [van Baal et al. 2012; da Costa et al.

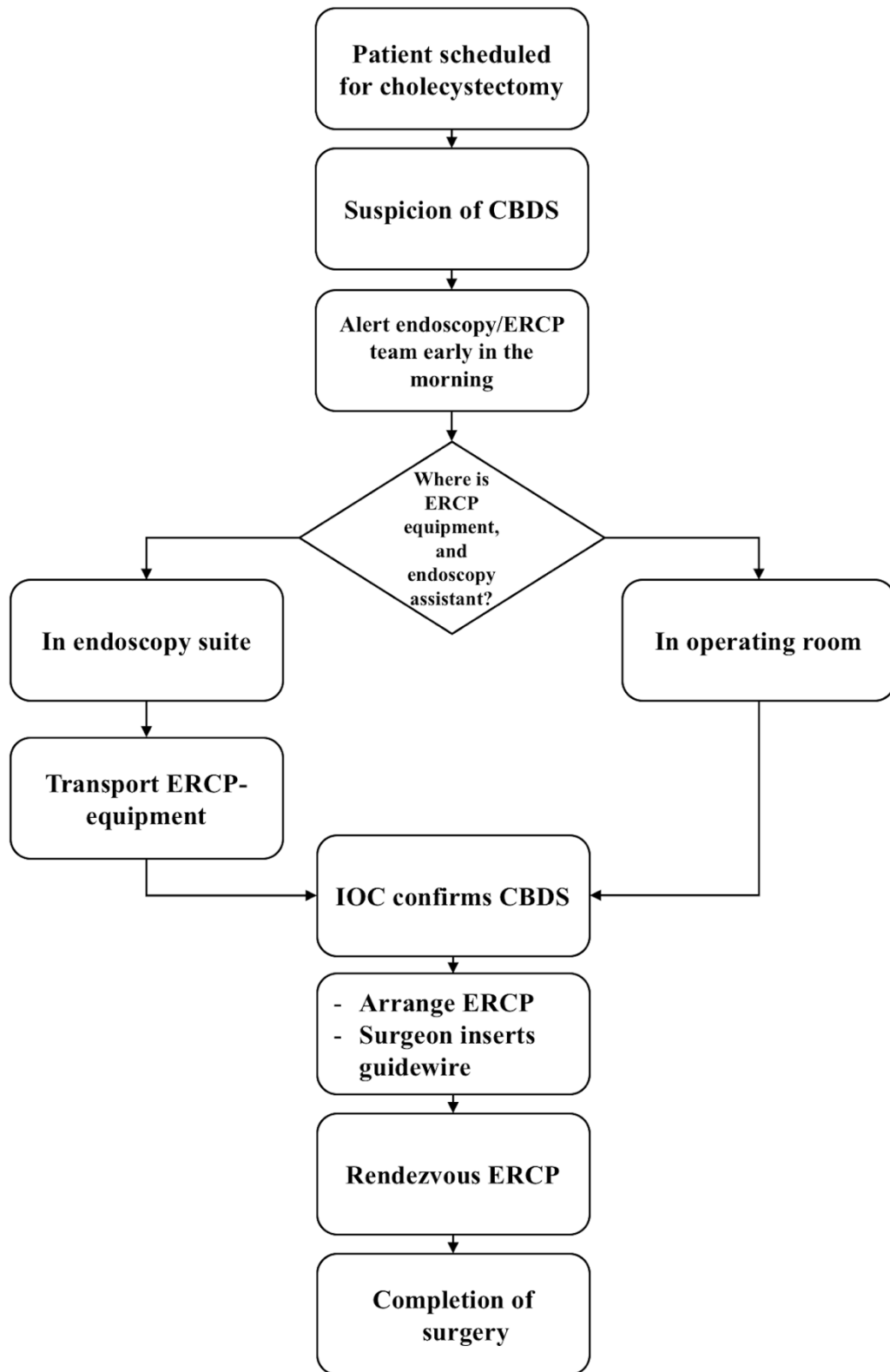
2015]. The clinical dilemma resides in the timing of the cholecystectomy in relation to the gallstone pancreatitis. Caution is still taken by surgeons when it comes to performing cholecystectomy in the setting of acute pancreatitis due to operative difficulties caused by the edema [Kelly and Wagner 1988; Aboulain et al. 2010].

The operative difficulty of the cholecystectomy and the risk of postoperative complications in the two settings have been assessed by indirect indicators such as operation time, conversion rate and more directly by a visual assessment of the difficulty of the cholecystectomy.

Previous randomized studies have not demonstrated differences in the difficulty of cholecystectomy assessed by operation time and conversion rates between patients who underwent cholecystectomy during the same admission and those who received a delayed cholecystectomy [Aboulain et al. 2010; da Costa et al. 2015]. Nevertheless, for a more precise comparison regarding the operative difficulty of the cholecystectomy an independent observer assessment of the difficulty of the cholecystectomy may be needed or larger scale studies with the power to detect these differences.

Aboulain et al. reported that early cholecystectomy may increase the risk to harbor CBDS at the IOC caused by stones that did not pass spontaneously into the duodenum. [Aboulain et al. 2010]. This imposes surgeons on another clinical dilemma of timing the ERCP with the cholecystectomy. In study IV, there was a higher rate (although not statistically significant) of CBDS at IOC in patients undergoing index cholecystectomy. The study is unique in a way that no preoperative sphincterotomy was practiced, resulting in dilution of the risk of biliary events for some patients. Thus, all patients who managed according to the study protocol had an equal risk of biliary complications.

To avoid additional risks of recurrent pancreatitis and other gallstone-related events it is recommended to perform cholecystectomy during the same admission.



**Figure 12.** A flowchart demonstrating practical details behind a successful rendezvous ERCP in the operating room. CBDS: common bile duct stones. ERCP: endoscopic retrograde cholangiopancreatography. IOC: intraoperative cholangiography.

## 6 SUMMARY:

The main findings in this thesis can be summarized:

- I. Intraoperative ERCP performed by the rendezvous technique during ongoing cholecystectomy is associated with low rate of post-ERCP pancreatitis.
- II. Cholecystectomy rates vary widely between the Swedish counties. Neither the high nor the changing cholecystectomy rate over time appear to prevent or reduce the risk for gallstone complications.
- III. Rendezvous ERCP performed for common bile duct stones during ongoing cholecystectomy is superior to the rendezvous ERCP performed postoperatively mainly because of the lower rates of post-ERCP pancreatitis and postoperative infections.
- IV. Delayed cholecystectomy in mild gallstone pancreatitis is associated with increased risk of gallstone-related complications.

## 7 CONCLUSIONS:

- I. When ERCP is chosen as a treatment option for common bile duct stones in the non-cholecystectomized and surgically fit patient, the rendezvous intraoperative ERCP is the method of choice. However, the technique requires functioning logistics and collaboration.
- II. Selecting patients with uncomplicated gallstone disease for cholecystectomy should be based on careful and sound clinical assesment.
- III. Rendezvous postoperative ERCP is a treatment option when common bile duct stones are detected during cholecystectomy and rendezvous intraoperative ERCP is hindered by logistical issues.
- IV. Patients with mild gallstone pancreatitis should undergo cholecystectomy during the same admission, as delaying the operation results in an increased risk for gallstone-related complications.



## 8 POPULÄRVETENSKAPLIG SAMMANFATTNING

Redan 2000 år före Kristus kom förmodligen den första beskrivningen av lever- och gallgångsanatomi i Mesopotamien, området runt Eufrat och Tigris. Människor gjorde levermodell av lera inklusive gallblåsa och gallgångar. Gallstenssjukdom är känd historiskt för att ha orsakat en hel del lidande, inte bara smärtor utan även döden. De första dokumenterade gallstenarna fann man i en egyptisk mumie.

Det var först under 1600-talet det hände något revolutionerande inom medicinhistoria, då ny kunskap om bl. a leverfunktionen kom och kännedom om att gallstenar orsakade sjukdom.

Gallstenar bildas hos cirka 10 – 20 % av befolkningen. Lyckligtvis är majoriteten av dessa människor utan besvär. Standardbehandling för symptomgivande gallstenar är borttagandet av gallblåsan. Gallstenar kan orsaka besvär i form av gallsmärtor (gallanfall) men också komplikationer i form av inflammation i gallblåsan, gallgången eller bukspottkörteln.

Första gallkirurgin, borttagande av gallblåsan utfördes av Berlinkirurgen Carl Langenbuch år 1882. Sedan dess har gallkirurgin tagit en annan utveckling. En ytterligare milstolpe inom gallkirurgin var introduktionen av tithålskirurgin år 1990. Borttagandet av gallblåsan är numera en av de vanligaste operationer och utförs som regel med tithålskirurgi.

Gallstenar kan också bildas i gallgången, men vanligast är att de migrerar från gallblåsan ned i gallgångarna. Till skillnad från gallblåsestenar, orsakar gallgångsstenar oftast besvär. De kan täppa till gallgången och orsaka gulsot, och oftast tillsammans med hög feber och ont i magen kallas det kolangit (infektion i gallgången). Migrerade gallstenar kan också orsaka stopp för bukspottkörtelflödet och ge upphov till akut pankreatit (akut inflammation i bukspottkörteln). Dessa tillstånd kräver oftast aktiv behandling i form av borttagandet av stenarna från gallgången.

Fram till 1968 genomgick patienter öppen kirurgi för borttagning av gallgångsstenar. Efteråt introducerades en endoskopisk teknik där man via en flexibel fiberoptisk slang kunde utföra mindre ingrepp på gallgångsöppningen och gallgången. År 1974 döptes denna teknik till ”ERCP” – endoskopisk retrograd kolangiopankreatografi. ERCP är numera en av de vanligaste metoderna för behandling av olika sjukdomar i gallgången inklusive gallstenar. För att kunna utföra behandlingar på gallgången behöver man först komma in i gallgången. Eftersom både gall- och bukspottkörtelgången delar mynning i tolvfingertarmen, kan man teoretiskt sett hamna oavsiktligt i bukspottkörtelgången. Detta kan utlösa post-ERCP pankreatit (PEP), som är en känd och befarad komplikation till ERCP. PEP förekommer i mindre än 4 % av alla ERCP procedurer.

Traditionellt sett har man utfört ERCP för gallgångsstenar före gallkirurgin. Detta är den vanligaste sättet internationellt. Eftersom de flesta stenar i gallgången passerar spontant till tarmen, är det vanligt att man inte hittar några stenar under ERCP:n. Dessutom behöver

patienter genomgå två ingrepp vilket medför ökad vårdtid. Det förekommer ibland att man inte lyckas komma in i gallgången, vilket innebär att man behöver utföra ett nytt ERCP försök eller ta patienten till operation.

Rutinmässigt utförs röntgen av gallgångssystemet under pågående galloperation för att dels ta redan på om det finns stenar i gångsystemet och dels för att se på gånganatomin. Det förekommer att man samtidigt hittar gallgångsstenar hos cirka 10 – 15 % av patienterna. Det finns flera olika metoder att behandla gallgångsstenar, varav ERCP är ett av de vanligaste sätten att behandla gallgångsstenar och kan fördelaktigt utföras under samma operation. En variant av ERCP har använts vid Karolinska Universitetssjukhuset i Huddinge sedan 1998. Det innebär att man under galloperationen placerar en metalltråd (ledare) genom gången som förbinder gallblåsan med resten av gallgångssystemet. När ledaren är på plats i tolvfingertarmen kan den användas som en guide för att underlätta tillträdet till gallgången via ERCP: n. Detta förfarande har minst två fördelar; först att man kommer in i gallgången selektivt utan att riskera komma in i bukspottkörtelgången och för det andra, har man nästan alltid en garanterad ingång i gallgången.

Denna ERCP teknik har fått namnet ”rendezvous” eftersom operatören och endoscopisten möts i tolvfingertarmen vid gallgångsöppningen.

I det första delarbetet studerades fördelarna med rendezvous-ERCP hos 307 patienter som genomgick galloperation och ERCP vid Karolinska Universitetssjukhuset i Huddinge under 10-års period. Det konstaterades att risken för att drabbas av PEP efter ERCP utfört med rendezvous teknik var betydligt lägre jämfört med när man har gjort ERCP på konventionellt sätt. Att behandla patienten under en och samma operation har ytterligare fördelar såsom kortare sjukhusvistelse, mindre kostnader och behov av en enda sövning.

Som tidigare nämnts, rekommenderas borttagandet av gallblåsan (vi kallar det galloperation för enkelhet) om man har besvär av sina gallstenar. Rekommendationen är dock stark om man har råkat för någon av gallstenskomplikationer, nämligen inflammation i gallblåsan eller inflammation i bukspottkörteln. Galloperationer utförs på ett stort antal svenska sjukhus runt om i landet. Det förekommer dock variationer i gallooperationsfrekvensen både nationellt och internationellt. Huruvida en hög operationsfrekvens kan förebygga gallstenskomplikationer genom att minska antalet individer med gallsten är inte känd. I det andra delarbetet studerades ett stort antal galloperationer från samtliga svenska län mellan 1998 och 2013. Frekvensen av gallooperationerna beräknades för varje län, justerad för kön och ålder. Dessutom studerades indikationerna för galloperationer mellan 2006 och 2013.

Studien påvisade att det förekommer stor variation i antal galloperationer mellan de svenska länen med en tvåfaldig skillnad mellan Örebro län (lägst) och Jämtland (högst). Det visades också att de länen med hög operationsfrekvens inte hade lägre gallstenskomplikationer. De flesta gallooperationerna utfördes på patienter med gallstenssmärtor utan komplikationer, vilket dominerades av kvinnor i unga åldrar. Däremot utfördes gallooperationer p.g.a. gallstenskomplikationer hos individer över 70 år.

Rendezvous-ERCP kan tekniskt sett utföras under pågående galloperation när befintlig logistik för sådant förfarande finns. Detta innebär att endoskopipersonal med deras utrustning behöver infinna sig på operationsavdelningen vid samma tidpunkt för ERCP:n. Om logistiken inte tillåter ERCP utförande på operationssalen, kan man placera och lämna ledaren i gallgången och avsluta galloperationen. Patienten planeras nästa dag för ett ERCP som fortfarande betraktas som rendezvous. Risken för komplikationer efter detta ERCP-förfarandet är inte studerad ännu. I tredje delarbetet, jämfördes både rendezvous-teknikerna med avseende på komplikationer. Studien visade att rendezvous ERCP utfört under samma operationstillfälle är överlägset bättre jämfört med den postoperativa rendezvous ERCP:n. Det förekom lägre risk för komplikationer i form av post-ERCP pankreatit (PEP) och infektioner.

När man drabbas av akut bukspottkörtelinflammation orsakad av gallsten, rekommenderas borttagandet av gallblåsan inom 2 – 4 veckor från det akuta insjuknandet. Hållfastheten till riktlinjerna varierar betydligt nationellt och internationellt. Tidpunkten för galloperationen har dock varit omdiskuterad. Patienter som inte får sin galloperation under samma inläggningstillfälle löper större risk att drabbas av en ny akut bukspottkörtelinflammation. Å andra sidan, har traditionen varit att avstå från galloperationen under pågående bukspottkörtelinflammation p.g.a. rädslan från en svår galloperation.

I fjärde delarbetet, har patienter med akut bukspottkörtelinflammation slumpmässigt valts (randomiserats) till antingen galloperation under samma inläggningstillfälle eller i ett senarelagd skede (minst 6 veckor efter insjuknandet). Det visades att patienter som fick vänta på sina galloperationer hade högre risk för att drabbas av en ny inflammation i bukspottkörteln jämfört med patienterna som opererades under samma inläggningstillfälle.

Sammanfattningsvis är ett äkta rendezvous-ERCP det som utföres med hjälp av en ledare. Tekniken medför färre bukspottkörtelinflammationer efter ERCP:n. Rendezvous-ERCP som är utfört under samma galloperation har lägre komplikationer jämfört med rendezvous-ERCP utfört efter galloperationen p.g.a. färre bukspottkörtelinflammationer och sårinfektioner.

Antalet galloperationer utförda i varje län varierar stort i Sverige. Varken den höga eller den ökande operationsfrekvensen visade förebyggande effekt på gallstenskomplikationer. Patienter som planeras för en senarelagd galloperation vid akut bukspottkörtelinflammation löper en större risk för en ny akut bukspottkörtelinflammation, därför bör galloperationen ske under samma inläggningstillfälle.

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